PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07D 233/22, A61K 31/4164, A61P 5/50, C07D 221/00, C07D 233/10, C07D 233/20, C07D 233/24, C07D 233/26, C07D 235/00, C07D 263/00, C07D 277/00, C07D 401/10, C07D 403/10, C07D 405/10, C07D 409/10, C07D 409/14, C07D 413/10, C07D 413/14, C07D 471/04, C07D 487/04, C07D 498/04, C07D 513/04

A1

(11) International Publication Number: WO 00/78726

(43) International Publication Date: 28 December2000 (28.12.2000)

(21) International Application Number: PCT/US00/11881

(22) International Filing Date: 19 June 2000 (19.06.2000)

(30) Priority Data:
9914222.6 18 June 1999 (18.06.1999) GB

(60) Parent Application or Grant
ELI LILLY AND COMPANY [/]; 0. PAAL, Michael [/]; 0. RUEHTER, Gerd [/]; 0. SCHOTTEN, Theo [/]; 0. PAAL, Michael [/]; 0. RUEHTER, Gerd [/]; 0. SCHOTTEN, Theo [/]; 0. VORNDRAN-JONES, MaCharri ; 0.

Published

(54) Title: IMIDAZOLINE DERIVATIVES FOR THE TREATMENT OF DIABETES, ESPECIALLY TYPE II DIABETES

(54) Titre: DERIVES D'IMIDAZOLINE POUR LE TRAITEMENT DU DIABETE, NOTAMMENT LE DIABETE DE TYPE II

(57) Abstract

This invention relates to certain novel imidazoline compounds and analogues thereof of Formula (I) wherein the group A is monocyclic or bicyclic ring, to their use for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present, to pharmaceutical compositions comprising them, and to processes for their preparation.

(57) Abrégé

Cette invention se rapporte à certains nouveaux composés d'imidazoline et à des analogues de ceux-ci, représentés par la formule (I), où le groupe A représente un noyau monocyclique ou bicyclique, à leur utilisation pour le traitement du diabète, des complications diabétiques, des troubles du métabolisme et des maladies apparentées, dans lesquelles apparaît une altération de la fonction d'élimination du glucose, à des compositions pharmaceutiques contenant ces composés et à des procédés pour leur préparation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78726 A1

(51) International Patent Classification[7]: C07D 233/22, A61K 31/4164, A61P 5/50, C07D 233/20, 409/10, 233/10, 405/10, 409/14, 401/10, 233/24, 471/04, 513/04, 487/04, 498/04, 413/10, 413/14, 403/10, 233/26 // (C07D 471/04, 235:00, 221:00) (C07D 513/04, 277:00, 235:00) (C07D 487/04, 235:00, 235:00) (C07D 498/04, 263:00, 235:00)

(21) International Application Number: PCT/US00/11881

(22) International Filing Date: 19 June 2000 (19.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9914222.6 18 June 1999 (18.06.1999) GB

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PAAL, Michael [DE/DE]; Hummelsbutteler Kirchenweg 11, D-22335 Hamburg (DE). RUEHTER, Gerd [DE/DE]; Vierzigstuecken 53A, D-21129 Hamburg (DE). SCHOTTEN, Theo [DE/DE]; Hinterm Bach 34, D-21444 Virhofen (DE).

(74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly And Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

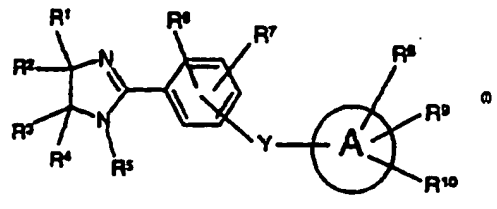
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/78726 A1

(54) Title: IMIDAZOLINE DERIVATIVES FOR THE TREATMENT OF DIABETES, ESPECIALLY TYPE II DIABETES



(57) Abstract: This invention relates to certain novel imidazoline compounds and analogues thereof of Formula (I) wherein the group A is monocyclic or bicyclic ring, to their use for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present, to pharmaceutical compositions comprising them, and to processes for their preparation.

Description

IMIDAZOLINE DERIVATIVES FOR THE TREATMENT OF DIABETES, ESPECIALLY TYPE II DIABETES

This invention relates to certain novel imidazoline-type compounds and analogues thereof, to their use for the treatment of diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present, to pharmaceutical compositions comprising them, and to processes for their preparation.

It is generally accepted that the control of blood glucose levels for the treatment of patients diagnosed with type II diabetes will have a beneficial effect. Established oral therapies for treating type II diabetes either improve insulin action or cause enhanced insulin secretion. Agents currently approved as therapies for type II diabetes patients that cause an enhanced insulin secretion contain a sulphonlyurea moiety. These compounds act by depolarising the beta cell by modulating closure of the K-ATP channel. Additional compounds that act at the K-ATP channel, which are not sulphonylureas compounds and which have a fast onset of activity and a short duration of action, are under consideration for treatment of type II diabetes. One such compound is (-)-N-(trans-4-isopropylcyclohexanecarbonyl)-D-phenylalanine (A-4166) (Brit. J. Pharm. 1997,120,137-145).

All agents that function at the molecular level by modulating the K-ATP channel have the potential for inducing hypoglycemia. Hypoglycemia is the major cause of adverse reactions in patients receiving sulphonylurea therapy and the prevalence of hypoglycemic episodes can be as high as 20% of patients. Compounds that potentiate insulin secretion under high glucose conditions and have little or no effect at low blood glucose levels would offer a distinct advantage in the treatment of type II diabetes.

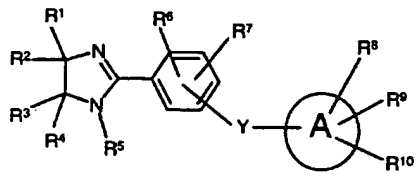
Compounds of the present invention potentiate the secretion of insulin from beta cells under high glucose conditions and have minimal effect under low glucose conditions.

The compounds are also operable in additional disease states where impaired glucose disposal is present. For example, these include cardiovascular disease where

above normal glucose levels are present or initial insulin resistance has occurred. The compounds can also be used to treat post operative insulin resistance induced by anaesthesia.

The present invention provides compounds of the following Formula (I), and the use of said compounds in the treatment of diabetes, especially Type II diabetes, diabetic complications, and metabolic disorders or related diseases in particular where impaired glucose disposal is present.

The present invention provides imidazoline compounds of the following Formula (I):



I

wherein

R^1, R^2, R^3, and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^3 and R^4, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

R^5 is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

R^6 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy;

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted phenyloxy, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_m$, $CH_3(CH_2)_p$-Z^1-$(CH_2)_q$-Z^2-, and Z^3-$(CH_2)_{q'}$-Z^2-;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  , SO_2, sulphoximino, or NR^{11};

Z^3 is hydroxy, protected hydroxy, $NR^{12}R^{13}$, protected amino, SH, or protected SH;

Y is selected from the group consisting of -NR'CONR''- or $-(CH_2)_kW(CH_2)_b$-, wherein $-(CH_2)_kW(CH_2)_b$-, is optionally substituted with C_{1-4} alkyl or hydroxy;

k is independently 0, 1, 2, 3, or 4;

b is independently 0, 1, 2, 3, or 4;

provided that the sum of k and b together is not more than 4;

W is selected from the group consisting of a bond, O, S, SO_2, SO, SO_2NR''', $NR'''SO_2$, NR'''', $CONR'''$, $NR'''CO$, -C=C-, -C≡C-, and C=O,

R', R'' and R''' are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and benzyl;

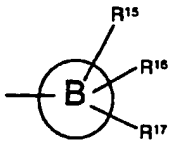
R'''' is selected from the group consisting of hydrogen, C_{1-8} alkyl, benzyl, and an amino protecting group;

the group A is a monocyclic or bicyclic ring selected from benzene, naphthalene, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, quinoline, isoquinoline, 1,5-naphthyridine, 1,6-naphthyridine, 1,7-naphthyridine, 1,8-naphthyridine, 2,6-naphthyridine, 2,7-naphthyridine, quinazoline, quinoxaline, phthalazine, cinnoline, furan, thiophene, benzofuran, benzo[b]thiophene, pyrrole, indole, imidazole, benzimidazole, imidazo[4,5-b]pyridine, imidazo[4,5-c]pyridine, oxazole, benzoxazole, oxazolo[5,4-b]pyridine, oxazolo[4,5-b]pyridine, oxazolo[5,4-c]pyridine, oxazolo[4,5-c]pyridine, isoxazole, 4,5-dihydroisoxazole, benzo[d]isoxazole, thiazole, benzothiazole, pyrazole, indazole, isothiazole, benzo[d]isothiazole, 1,2,3-triazole, benzotriazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, benzo[1,2,5]oxadiazole, 1,3,4-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,2,3-thiadiazole, benzo[1,2,5]thiadiazole, 1H-tetrazole, imidazo[1,2-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-b]pyridazine, imidazo[1,2-a]pyrimidine, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole, imidazo[1,2-a]imidazole,

which may be fused with a benzene ring to form a tricyclic ring;

R^8 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkynyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, cyano, nitro, formyl, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl,

optionally substituted phenyl C_{1-8} alkoxy, C_{1-8} alkylthio, optionally substituted benzylthio, CH_2OH, amino, NHCO C_{1-8} alkyl, $CONR^{12}R^{13}$, $CONHR^{14}$, $CH_3(CH_2)_r$-O-$(CH_2)_s$-O-, $CH_3(CH_2)_t$-O-$(CH_2)_u$-O-CH_2, and a group of Formula (II)



II

wherein

the ring B is selected from benzene, naphthalene, pyridine, furan, benzofuran, thiophene, or benzo[b]thiophene;

R^9 and R^{10} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, CH_2OH, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl, optionally substituted benzyloxy;

R^{11}, R^{12}, and R^{13} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, and optionally substituted phenyl;

R^{12} and R^{13} together with the nitrogen atom to which they are attached optionally combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkylene, wherein the C_{2-6} alkylene is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by oxygen or sulfur;

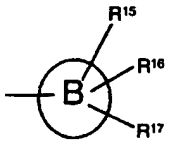
R^{14} is an amino acid residue selected from glycine, alanine, leucine, isoleucine, methionine, phenylalanine, or valine in which the carboxylate may form a carboxylic acid or a C_{1-8} alkyl ester;

R^{15} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, C_{1-8} alkylthio, amino, NHCO C_{1-8} alkyl, optionally substituted NHCO phenyl, optionally substituted phenyl;

R^{16} and R^{17} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy;

p, r, and t are each independently selected a number consisting of 0, 1, 2, 3, or 4;
q, q', s, and u are each independently a number consisting of 1, 2, 3, 4, or 5;
m and m' are each independently a number consisting of 0, 1, or 2;

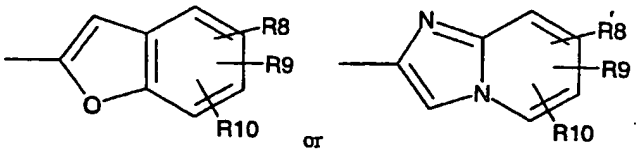
and provided that when Y is a bond or –O- and A is benzene and only one selected from the group consisting of R^8, R^9 and R^{10} is a non-hydrogen group, then at least one selected from the group consisting of R^8, R^9 and R^{10} is selected from the group consisting of C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} alkoxy, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cycloalkyl, cyano, nitro, formyl, carbo C_{1-8} alkoxy, substituted phenyl, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted benzylthio, amino, NHCO C_{1-8} alkyl, $CONR^{12}R^{13}$, $CONHR^{14}$, $CH_3(CH_2)_r$-O-$(CH_2)_s$-O-, $CH_3(CH_2)_t$-O-$(CH_2)_u$-O-CH_2, and a group of Formula (II)



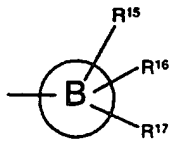
II

B is selected from the group consisting of benzene, wherein at least one selected from the group consisting of R^{15}, R^{16} and R^{17} is a non-hydrogen group when B is benzene, naphthalene, pyridine, furan, benzofuran, thiophene, or benzo[b]thiophene;

or when Y is a bond and A is a group of the formula



then R^8 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkynyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, nitro, formyl, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, C_{1-8} alkylthio, optionally substituted benzylthio, CH_2OH, amino, NHCO C_{1-8} alkyl, $CONR^{12}R^{13}$, $CONHR^{14}$, $CH_3(CH_2)_r$-O-$(CH_2)_s$-O-, $CH_3(CH_2)_t$-O-$(CH_2)_u$-O-CH_2, and a group of Formula (II)



II; and

pharmaceutically acceptable salts and esters thereof.

One embodiment of the present application is the use of a compound of the Formula I or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for treating diabetes or a related disorder.

Another embodiment of the present invention is a method of treating diabetes or a related disorder, which comprises administering to a patient a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In the above formulae, a "C_{1-8} alkyl" group can be any alkyl group, branched or unbranched, containing up to eight carbon atoms, likewise, $C_{1-n'}$ alkyl is a branched or unbranched alkyl containing up to n' carbon atoms whereing n' is an integer. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary

butyl, pentyl and hexyl. Preferred values of C_{1-8} alkyl are C_{1-6} alkyl, and most preferably methyl and ethyl.

The term "C_{1-8} alkylthio" has the meaning known to the artisan. That is that one of the carbon atoms is replaced with a sulfur atom.

A "C_{3-7} cycloalkyl" group is a saturated carbon ring having from 3 to 7 carbon atoms. Such groups include, but are not limited to, as cyclopropyl, cyclobutyl, cycloheptyl, cyclohexyl or cyclopentyl.

A "C_{3-7} cycloalkyl-C_{1-8} alkyl" group is one wherein the cycloalkyl group is attached through a C_{1-8} alkyl group to the base molecule. It is especially preferred that the alkyl group is C_{1-6} alkyl.

A "C_{1-8} alkoxy" group is one of the above-mentioned C_{1-8} alkyl groups attached through oxygen to the base molecule, and preferred examples are methoxy and ethoxy.

A "C_{3-7} cycloalkoxy" group is a C_{3-7} cycloalkyl group as mentioned above linked through an oxygen atom to the cycloalkyl as, for example, cyclopropyloxy, cyclopentyloxy and cyclohexyloxy.

A "C_{3-7} cycloalkylC_{1-8} alkoxy" group is a C_{3-7} cycoalkyl-C_{1-8} alkyl as mentioned above linked through an oxygen atom to the base molecule as, for example, cyclohexylmethoxy.

A "carbo(C_{1-8})alkoxy" group is a $-\overset{O}{\overset{\|}{C}}-OC_{1-8}alkyl$ group, for example a carbomethoxy or carboethoxy group.

An "optionally substituted aryl" group is a mononuclear or polynuclear aromatic hydrocarbon group, for example phenyl or naphthyl, which is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl,

alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino., carboxy, hydroxy,

An "optionally substituted phenyl" group is a phenyl which is optionally substituted with from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl, alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted benzylthio" group is a benzylthio which is optionally substituted with from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl, alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted benzyloxy" group is a benzyloxy which is optionally substituted with from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents independently selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} alkoxy, alkoxyhydroxymethyl, alkoxy hydroxyformyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted naphthyl" group is a naphthyl which is optionally substituted with from one to three substituents independently selected from, the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl,

SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "optionally substituted COaryl" group is an optionally substituted aryl which is bound to the base molecule through a group of the formula:  . The optionally substituted aryl group is defined herein above.

A "optionally substituted aryl-C_{1-8} alkyl-$S(O)_m$- " group is an optionally substituted aryl which is bound to the base molecule through an alkyl-$S(O)_m$- group, wherein the S- bonds to the base molecule. The optionally substituted aryl group is as defined herein above.

An "optionally substituted heteroaryl" group is a heteroaryl group which is optionally substituted with from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, alkoxy carbonyl, formyl, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, amino, and phenyl which is optionally substituted by from one to three substituents each independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro, phenyl, 3,4-methylenedioxy, and amino.

An "aryl-C_{1-8} alkyl" group can be, for example, optionally substituted phenyl-C_{1-8} alkyl or optionally substituted naphthyl-C_{1-8} alkyl, such optionally substituted phenyl or naphthyl groups being optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino. A preferred aryl-C_{1-8} alkyl group is optionally substituted phenyl-$(CH_2)_x$- where x is 1 or 2, most preferably optionally substituted benzyl. Thus, the alkyl group serves as the link between the phenyl or naphtyl and the base molecule.

An "optionally substituted phenyloxy" is a group wherein the phenyl group is attached to the base molecule through an oxygen, and such phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino.

The term "non-hydrogen group" means a substituent selected from the group of potential substituents for a given base molecule in which at least one atom of the substituent is carbon or a heteroatom other than hydrogen.

An "optionally substituted phenylC_{1-8} alkoxy" is a group wherein the phenyl group is attached to the base molecule through an alkoxy group, and such phenyl group is optionally substituted with one or more, preferably one to three, substituents selected from, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino.

Of course, it will be understood that "optionally substituted" means that there may be zero non-hydrogen substituents.

An "aryl-C_{1-8} alkoxy" group can be, for example, optionally substituted phenyl-C_{1-8} alkoxy or optionally substituted naphthyl-C_{1-8} alkoxy, such optionally substituted groups being optionally substituted with one or more, preferably one to three, substituents selected from, for example, C_{1-8} alkyl, C_{1-8} alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, SCH_3, nitro and amino. A preferred aryl-C_{1-8} alkyl group is optionally substituted phenyl-$(CH_2)_x$- where x^- is 1 or 2. Thus, the aryl is linked to the base molecule through the alkoxy group.

A halo group is preferably chloro, bromo or fluoro.

A "halo C_{1-8} alkyl" or "halo C_{1-8} alkoxy" or "halo C_{1-8} alkylthio" is a substituent in which one or more, preferably one to three, hydrogen atoms on the C_{1-8} alkyl moiety is replaced by a halo atom, preferably chloro, bromo or fluoro. Trifluoromethyl is one preferred haloalkyl group.

An "alkoxyalkoxy" group is of the formula $CH_3(CH_2)_p$-O-$(CH_2)_q$-O-, where p is 0-4 and q is 1-5, preferred examples being those in which p is 0 or 1 and q is 1-3, especially methoxyethoxy, ethoxyethoxy, ethoxypropoxy, or methoxypropoxy.

The term "spirocarbocyclic" means a ring which is fused to the base molecule through one shared tetravalent carbon atom to form two rings which are annelated by a single carbon atom.

The "acyl" moiety, alone or in combination, is derived from an alkanoic acid containing from one to eight carbon atoms. The term "acyl" also includes moieties derived from an aryl carboxylic acid or heteroaryl.

As used herein, the term "aryl coupling" shall mean any appropriate method for coupling two aromatic or heteroaromatic rings known to the artisan. Such methods may include, but are not limited to Ullmann, Stille coupling or Suzuki coupling methods. The Suzuki coupling is an especially preferred coupling method. The Suzuki method using aryl boronic acid derivatives, e.g. Ar-$B(OH)_2$ and Pd catalyst is particularly preferred for use in the synthesis methods described herein. The artisan will appreciate that there are a variety of available Pd catalysts which are acceptable for the Suzuki coupling. One such Pd catalyst which is preferred for the methods described herein is $Pd(PPh_3)_4$.

The artisan will also appreciate that there are a variety of available metal catalysts other than Pd which are acceptable for aryl coupling reactions.

The term "base molecule" means the ring system to which the named substituent is bound.

The term "treating", as used herein, describes the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of a compound of present invention to prevent the onset of the symptoms or complications, to alleviate the symptoms or complications, or to eliminate the disease, condition, or disorder.

As used herein the term "amino protecting group" means any of the conventional amino protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 7, John Wiley and Sons, New York, 1981, and

by J. W. Barton, Protective Groups in Organic Chemistry, chapter 2, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to benzyl and substituted benzyl such as 3,4-dimethoxybenzyl, o-nitrobenzyl, and triphenylmethyl; those of the formula -COOR where R includes such groups as methyl, ethyl, propyl, isopropyl, 2,2,2-trichloroethyl, 1-methyl-1-phenylethyl, isobutyl, t-butyl, t-amyl, vinyl, allyl, phenyl, benzyl, p-nitrobenzyl, o-nitrobenzyl, and 2,4-dichlorobenzyl; acyl groups and substituted acyl such as formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, benzoyl, and p-methoxybenzoyl; and other groups such as methanesulfonyl, p-toluenesulfonyl, p-bromobenzenesulfonyl, p-nitrophenylethyl, p-toluenesulfonylaminocarbonyl, and the like. Preferred nitrogen protecting groups are benzyl, acyl, like benzyloxycarbonyl or t-butyloxycarbonyl, or silyl or acetyl phenyloxycarbonyl.

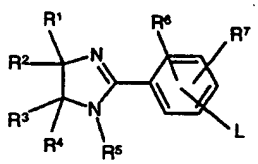
The term "protected amino" means that the amino group is substituted with an amino protecting group, as defined herein.

As used herein the term "protected hydroxy" means that the hydroxyl group is substituted with any of the conventional hydroxyl protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 2, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups include but are not intended to be limited to acetals, ethers such as silyl ethers and the like; esters such as formate, benzoylformate, acetate, phenoxyacetate and the like; carbonates such as methyl carbonate, ethyl carbonate, isobutylcarbonate, benzyl, nitrobenzyl, and the like; and others such as nitrate, borate, phenylcarbamate, tetrahydropyranyl (THP), trityloxypyrinyl and the like. The artisan will recognise that the art includes other acceptable protecting groups as provided by the cited references.

As used herein the term "protected SH" means that the thiol group is substituted with any of the conventional thiol protecting groups, see, for instance, T. W. Greene, Protective Groups in Organic Synthesis, chapter 6, John Wiley and Sons, New York, 1981, and by J. W. Barton, Protective Groups in Organic Chemistry, J. F. W. McOmie, ed., Plenum Press, New York, 1973. Examples of such groups

include but are not intended to be limited to thioethers like benzylthioether, 4-methylbenzylthioether, p-nitrobenzylthioether, diphenylmethylthioether, substituted methyl derivatives such as methoxymethyl (MOM), isobutoxymethyl, 2-tetrahydropyranyl, thioesters like, acetyl, benzoyl, thiocarbonates like t-butoxycarbonyl, and the like.

The compounds of the present invention can be useful for modulating insulin secretion and as research tools. Certain compounds and conditions within the scope of this invention are preferred. The following embodiments of this invention is not intended to limit the scope of this invention in any way Another embodiment of the present invention are compounds of Formula III which may be used as intermediates to prepare compounds of Formula I in which the group Y is a bond,



III

wherein R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are defined in the same manner as in Formula I and L is selected from bromo, iodo, or fluoro C_{1-4} alkylsulfonyloxy.

Preferred groups L are bromo, iodo, and trifluromethylsulfonyloxy, most preferred bromo.

In preferred compounds of the present invention R^1, R^2, R^3, and R^4 are independently selected from hydrogen, methyl, or ethyl. In more preferred compounds R^1 and R^2 are methyl and R^3 and R^4 are hydrogen, or R^3 and R^4 are methyl and R^1 and R^2 are hydrogen, or R^1, R^2, R^3, and R^4 are hydrogen.

R^5 is preferably hydrogen or an amino protecting group. Particularly preferred R^5 is hydrogen.

In most preferred compounds of the present invention all substituents R^1, R^2, R^3, R^4, and R^5 at the imidazoline ring are hydrogen.

Preferred groups Y are a bond, CONH, NHCO, $N(CH_3)CO$, $CON(CH_3)$, OCH_2, CH_2O, O, S, SO_2, NH, NCH_3, NHCONH, $NHSO_2$, SO_2NH, $N(CH_3)SO_2$, $SO_2N(CH_3)$, CHOH, -C=C-, -C≡C-, or C=O, more preferred a bond, CONH, NHCO, OCH_2, CH_2O, O, SO_2, or -C≡C-. Mostly preferred the group Y is a bond.

Preferred substituents R^6 are selected from hydrogen, halo, methyl, ethyl, trifluoromethyl, methoxy, ethoxy, more preferred hydrogen, fluoro, or chloro, mostly preferred hydrogen.

Preferred substituents R^7 are selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, benzyloxy, hydroxy, halo, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkylthio, $CH_3(CH_2)_{p''}$-O-$(CH_2)_{q''}$-O-, in which p'' is 1 or 2 and q'' is 2 or 3. More preferred substituents R^7 are hydrogen, methyl, ethyl, propyl, butyl, propoxy, butoxy, CH_3CH_2-O-$(CH_2)_2$-O-, or CH_3-O-$(CH_2)_2$-O-.

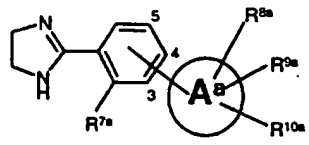
In most preferred compounds of the present invention R^6 and R^7 are both hydrogen or R^6 is hydrogen and R^7 is CH_3-O-$(CH_2)_2$-O-.

Preferred carbocyclic or heterocyclic rings A in compounds of Formula I are benzene, naphthalene, pyridine, pyrimidine, quinoline, isoquinoline, furan, thiophene, benzofuran, naphtho[2,1-b]furan, benzo[b]thiophene, pyrrole, indole, imidazole, benzimidazole, oxazole, benzoxazole, isoxazole, 4,5-dihydroisoxazole, thiazole, benzothiazole, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazole, imidazo[1,2-a]benzimidazole, imidazo[2,1-b]benzoxazole, imidazo[2,1-b]benzothiazole;

more preferred benzene, naphthalene, thiophene, benzofuran, pyrrole, isoxazole, 4,5-dihydroisoxazole, imidazo[1,2-a]pyridine;

mostly preferred benzene or benzofuran.

The following compounds of Formula Ia to Formula Ir are preferred:



(i) Ia

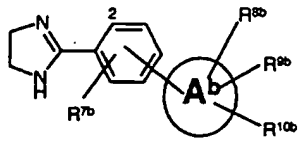
wherein

the ring A^a is selected from benzene, naphthalene, or thiophene which are attached to the indicated positions 3, 4, or 5 of the benzene ring;

R^{7a} is C_{1-8} alkoxy or $CH_3(CH_2)_{p^a}$-O-$(CH_2)_{q^a}$-O-, in which p^a is a number 0, 1, 2, 3, or 4, and q^a is a number 1, 2, 3, 4, or 5;

R^{8a}, R^{9a}, and R^{10a} are each independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy.

In more preferred compounds of Formula Ia R^{7a} is CH_3-O-$(CH_2)_2$-O-, and the ring A^a together with the substituents R^{8a}, R^{9a}, and R^{10a} is selected from phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 5-chloro-2-thienyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 4-methylphenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 3,5-dichlorophenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3-chloro-4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3,5-bistrifluoromethylphenyl, 3-nitrophenyl.



(ii) Ib

wherein

the ring A^b is selected from benzene, naphthalene, thiophene, pyridine, quinoline, or isoquinoline;

R^{7b} is hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, halo C_{1-8} alkyl, or halo;

R^{8b} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy, C_{1-8} alkylthio, CH_2OH, amino, NHCO C_{1-8} alkyl, $CONR^{12b}R^{13b}$, $CH_3(CH_2)_{r'}$-O-$(CH_2)_{s'}$-O-, $CH_3(CH_2)_{t'}$-O-$(CH_2)_{u'}$-O-CH_2-;

R^{9b} and R^{10b} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy;

R^{12b} and R^{13b} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, and optionally substituted phenyl, or R^{12b} and R^{13b} together with the nitrogen atom to which they are attached may combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkylene, wherein the C_{2-6} alkylene is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by oxygen or sulfur;

r' and t' are each independently a number consisting of 0, 1, 2, 3, or 4;

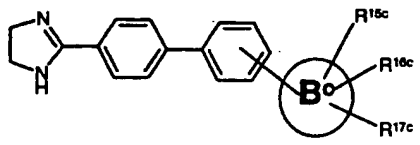
s' and u' are each independently a number consisting of 1, 2, 3, 4, or 5;

with the proviso that R^{7b}, R^{8b}, R^{9b}, and R^{10b} together are not hydrogen, if the ring A^b is benzene.

In more preferred compounds of Formula Ib R^{7b} is hydrogen or C_{1-4} alkyl, particularly preferred hydrogen or methyl which is preferably attached to the indicated position 2 of the benzene ring.

In more preferred compounds of Formula Ib the ring A^b together with the substituents R^{8b}, R^{9b}, and R^{10b} is selected from 1-naphthyl, 2-naphthyl, 2-thienyl, 3-thienyl, 5-chloro-2-thienyl, isoquinolin-4-yl, pyridin-3-yl, 2-methoxyphenyl, 3-

methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3,5-bistrifluoromethylphenyl, 3-nitrophenyl, 4-nitrophenyl, 2-aminophenyl, 3-aminophenyl, 4-hydroxyphenyl, 4-(hydroxymethyl)phenyl, 4-bromophenyl, 4-ethylphenyl, 4-heptylphenyl, 4-pentylphenyl, 4-cyanophenyl, 4-(methylthio)phenyl, 4-(hydroxycarbonyl)phenyl, 4-(methoxycarbonyl)phenyl, 4-(ethoxycarbonyl)phenyl, 2-(1-buten-1-yl)phenyl, 3-(1-buten-1-yl)phenyl, 4-(1-buten-1-yl)phenyl, 4-(N-phenylaminocarbonyl)phenyl, 4-(N-hexylaminocarbonyl)phenyl, 3-(acetylamino)phenyl, 4-(2-methoxyethoxy)phenyl, 4-(2-methoxyethoxy)methylphenyl.

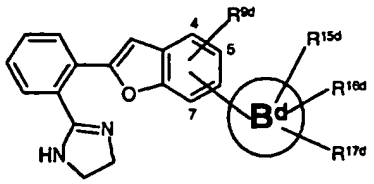
(iii)  Ic

wherein

the ring B^c is selected from benzene, naphthalene, or thiophene;

R^{15c}, R^{16c}, and R^{17c} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, nitro, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula Ic the ring B^c together with the substituents R^{15c}, R^{16c}, and R^{17c} is selected from phenyl, 2-thienyl, 3-thienyl, 5-chloro-2-thienyl, 2-methoxyphenyl, 4-methylphenyl, 4-fluorophenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,5-bistrifluoromethylphenyl, 3-nitrophenyl, 2,4,6-trimethylphenyl.



(iv) **Id**

wherein

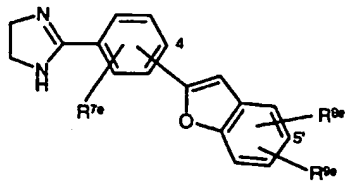
the ring B^d is selected from benzene, naphthalene, or thiophene which are attached to the indicated positions 4, 5, or 7 of the benzofuran ring;

R^{9d} is hydrogen, C_{1-8} alkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, or halo;

R^{15d} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy, C_{1-8} alkylthio, amino, NHCO C_{1-8} alkyl;

R^{16d} and R^{17d} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula Id R^{9d} is hydrogen, fluoro, chloro, methyl, trifluoromethyl, or methoxy, particularly preferred hydrogen, and B^d together with the substituents R^{15d}, R^{16d}, and R^{17d} is selected from phenyl, 2-thienyl, 3-thienyl, 5-chloro-2-thienyl, 1-naphthyl, 2-naphthyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 4-methylphenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 2,4-dichlorophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3,5-bistrifluoromethylphenyl, 3-nitrophenyl, 2,4,6-trimethylphenyl, 3-aminophenyl, 3-chloro-4-fluorophenyl, 4-(methylthio)phenyl, 3-(acetylamino)phenyl.



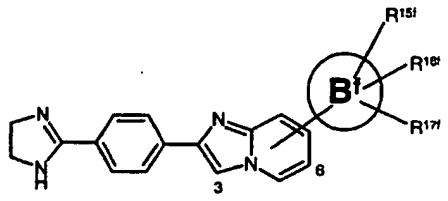
(v) Ie

wherein

R^{7e}, R^{8e}, and R^{9e} are independently selected from hydrogen, C_{1-8} alkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, or halo;

with the proviso that R^{8e} or R^{9e} are not bromo, if they are attached to the indicated position 5' of the benzofuran ring and the other one of both as well as R^{7e} is hydrogen, and if the benzofuran ring is attached to the indicated position 4 of the benzene ring.

In more preferred compounds of Formula Ie R^{7e} is hydrogen, fluoro, or chloro, particularly preferred hydrogen, and R^{8e} and R^{9e} each are independently hydrogen, fluoro, chloro, bromo, methyl, methoxy, or trifluoromethyl, particularly preferred hydrogen or bromo.



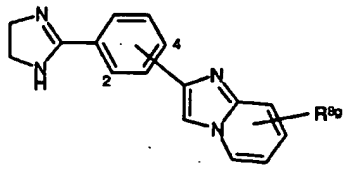
(vi) If

wherein

the ring B^f is selected from benzene, naphthalene, benzofuran, or thiophene which are attached to the indicated positions 3 or 6 of the imidazo[1,2-a]pyridine ring;

R^{15f}, R^{16f}, and R^{17f} are each independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula If the ring B^f together with the substituents R^{15f}, R^{16f}, and R^{17f} is selected from phenyl, 2-thienyl, 3-thienyl, 1-naphthyl, 2-naphthyl, 2-benzofuranyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-methylphenyl, 2,4-dichlorophenyl.



(vii) Ig

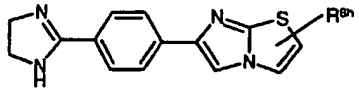
wherein

the imidazo[1,2-a]pyridine ring is attached to the indicated positions 2 or 4 of the benzene ring;

R^{8g} is selected from hydrogen, C_{1-8} alkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy;

with the proviso that R^{8g} is not hydrogen, if the imidazo[1,2-a]pyridine ring is attached to position 4.

In more preferred compounds of Formula Ig R^{8g} is hydrogen, fluoro, chloro, bromo, methyl, methoxy, or benzyloxy.

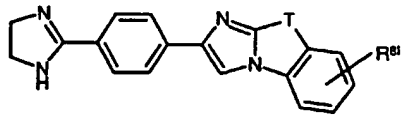


(viii) Ih

wherein

R^{8h} is selected from hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, halo, optionally substituted benzyloxy.

In more preferred compounds of Formula Ih R^{8h} is hydrogen, fluoro, chloro, bromo, methyl, particularly preferred hydrogen.



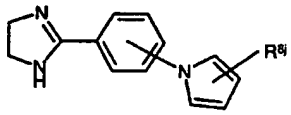
(ix) Ii

wherein

the group T is selected from -O-, -S-, -NH-, and -N C_{1-4} alkyl-;

R^{8i} is selected from hydrogen, C_{1-8} alkyl, C_{3-7} cycloalkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, cyano, nitro, halo, optionally substituted benzyloxy.

In more preferred compounds of Formula Ii the group T is -O-, -S-, -NH-, and $-NCH_3$-, particularly preferred -S-, and R^{8i} is hydrogen, chloro, methyl, or methoxy.

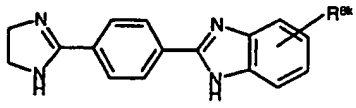


(x) Ij

wherein

R^{8j} is selected from hydrogen, C_{1-8} alkyl, halo C_{1-8} alkyl, cyano, nitro, halo, formyl.

In more preferred compounds of Formula Ij R^{8j} is hydrogen or formyl.

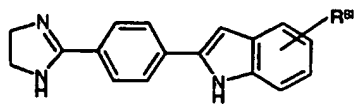


(xi) Ik

wherein

R^{8k} is selected from hydrogen, C_{1-8} alkyl, halo C_{1-8} alkyl, cyano, nitro, halo, hydroxy, C_{1-8} alkoxy, optionally substituted benzyloxy.

In more preferred compounds of Formula Ik R^{8k} is hydrogen, chloro, hydroxy, methyl, or methoxy, particularly preferred hydrogen.

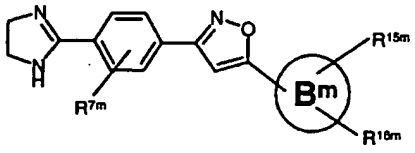


(xii) II

wherein

R^{8l} is selected from hydrogen, C_{1-8} alkyl, halo C_{1-8} alkyl, C_{1-8} alkoxy, cyano, halo.

In more preferred compounds of Formula Il R^{8l} is hydrogen or chloro.



(xiii) Im

wherein

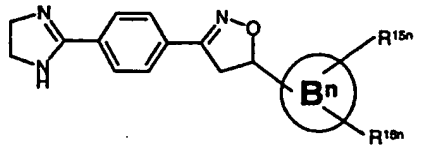
the ring B^m is selected from benzene, naphthalene, or pyridine;

R^{7m} is selected from hydrogen or halo;

R^{15m} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy;

R^{16m} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula Im R^{7m} is hydrogen and the ring B^m together with the substituents R^{15m} and R^{16m} is selected from phenyl, 2-pyridinyl, 4-methoxyphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-propoxyphenyl, 3-benzyloxyphenyl, 4-propoxyphenyl, 4-methylphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-trifluoromethylphenyl, 2-ethylphenyl, 4-butylphenyl.



(xiv) In

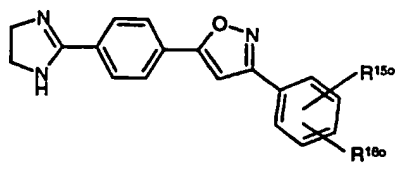
wherein

the ring B^n is selected from benzene, naphthalene, or pyridine;

R^{15n} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy, amino, NHCO C_{1-8} alkyl, optionally substituted NHCO phenyl, optionally substituted phenyl;

R^{16n} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula In the ring B^n together with the substituents R^{15n} and R^{16n} is selected from phenyl, 2-naphthyl, 4-methylphenyl, 3-methylphenyl, 2-methylphenyl, 2,4-dimethylphenyl, biphenyl, 3-chlorophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 2,6-difluorophenyl, 4-aminophenyl, 4-(benzoylamino)phenyl, 4-(hydroxycarbonyl)phenyl, 4-(ethoxycarbonyl)phenyl.



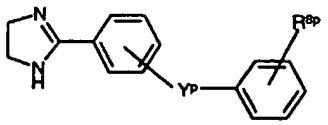
(xv) Io

wherein

R^{15o} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted benzyloxy, optionally substituted phenyl;

R^{16o} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula **Io** the phenyl ring together with the substituents R^{15o} and R^{16o} is selected from phenyl, biphenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 2-bromophenyl.



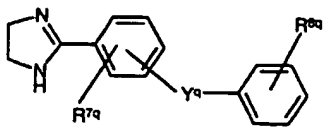
(xvi) Ip

wherein

the group Y^p is OCH_2 or CH_2O;

R^{8p} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, nitro, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula **Ip** R^{8p} is hydrogen or methoxy.



(xvii) Iq

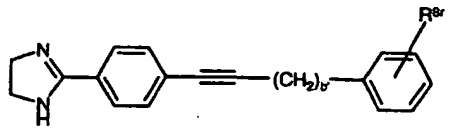
wherein

the group Y^q is NHCO, NHCONH, or CONH;

R^{7q} is hydrogen or halo;

R^{8q} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, nitro, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula Ip R^{7q} and R^{8q} are independently hydrogen or fluoro.



(xviii) Ir

wherein

b' is 0, 1, 2, or 3;

R^{8r} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy.

In more preferred compounds of Formula Ir R^{8r} is hydrogen, methyl, or ethyl.

The artisan will recognise that there are a number of processes which could be used to prepare desired imidazoline compounds. See for example, J.Med.Chem. 1990, 33, 2501-8 (uses $(CH_2NH_2)_2$); J.Chem.Soc. 1947, 497 (uses $(CH_2NH_2)_2$ and TsOH/200-220^{0}C); J.Am.Chem.Soc. 1953, 75, 2986-8 (uses $(CH_2NH_2)_2$ and 200-220^{0}C); J.Med.Chem. 1987, 30, 1482-9 (uses $Al(CH_3)_3$ and $(CH_2NH_2)_2$); Tetrahedron Lett. 1990, 31, 1771-74 (uses $(CH_2NH_2)_2$); J.Org.Chem. 1987, 52, 1017-21 ($La(OSO_2CF_3)_3$ and $(CH_2NH_2)_2$); Zh.Prikl.Khim. 1970, 43, 1641 (CA:73:77138r)

(uses $(CH_2NH_2)_2$ and strongly acidic cation exchange reagent); Arch.Pharm. 1986, 319, 830-34 (uses $(CH_2NH_2)_2$); J.Heterocycl.Chem. 1990, 27, 803-5 (uses $(CH_2NH_2)_2$); Tetrahedron 1995, 51, 6315-36 (uses two step process with 1) H_2S and H_3Cl then 2)$(CH_2NH_2)_2$).

Preferred methods to form an imidazoline ring are:

1) treatment of a benzonitrile of Formula IV (G = cyano) with hydrochloric acid in an alcohol like methanol or ethanol followed by reaction with a diamine of Formula V, preferably with 1,2-diaminoethane

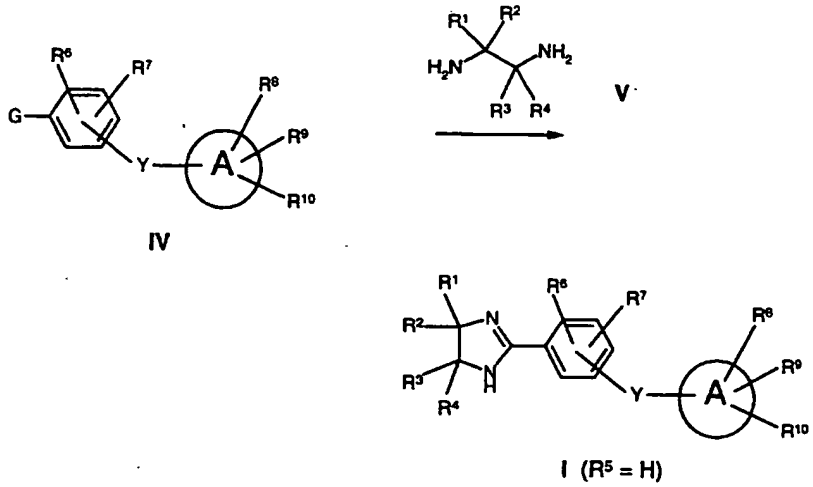
2) heating of a benzonitrile of Formula IV (G = cyano) with a diamine of Formula V in the presence of p-toluenesulfonic acid at temperatures 200 – 220 °C

3) heating of a benzonitrile of Formula IV (G = cyano) with a diamine of Formula V in the presence of a catalytic amount of carbon disulfide, preferably in neat 1,2-diaminoethane

4) heating of an 2-aminoethyl amide of Formula VI with $POCl_3$

General methods of synthesis for the compounds of the present invention are described in Schemes below.

Scheme I

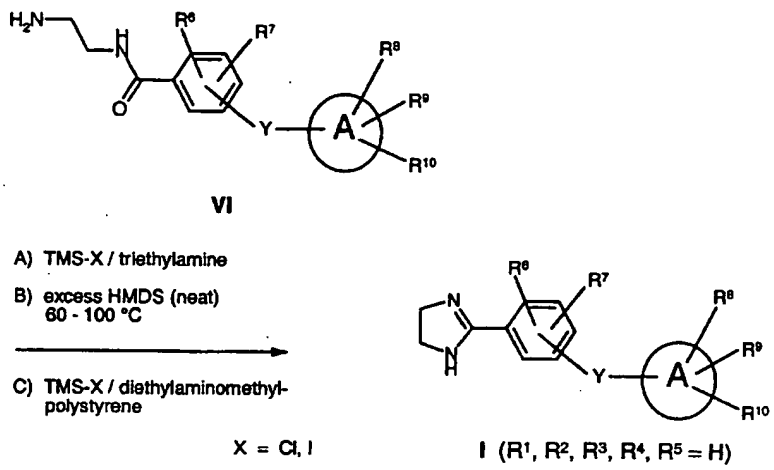


Scheme I describes the formation of an imidazoline ring in compounds of Formula I where R^5 is hydrogen from 1,2-diamino compounds of Formula V and intermediates of Formula IV, in which the group G is a suitable precursor for an imidazoline. The artisan will appreciate that this transformation indicated in Scheme I can also be carried out to prepare any other precursor of compounds of Formula I which contains an imidazoline ring and which may be used to prepare compounds of Formula I by manipulation of any substituent R^6 or R^7 attached to the benzene ring or R^8 to R^{17} attached to the rings A or B. In particular, these methods may also be used to prepare phenylimidazoline intermediates for the synthesis of compounds of Formula I which are formed by reaction with intermediates containg the ring A under formation of the group Y. Preferred groups G are cyano, carboxy, or carbo C_{1-8} alkoxy.

In a specific preferred procedure the transformation of an 2-aminoethyl amide VI to an imidazoline may also be carried out with a silylating agent. This transformation is outlined in Scheme II for the case in which R^1, R^2, R^3, and R^4 are hydrogen, but it may also be carried out for cases in which R^1, R^2, R^3, and R^4 are any

other substituent according to Formula I. The 2-aminoethyl amides VI are preferably obtained from intermediates of Formula IV in which G is carbo C_{1-8} alkoxy by heating with 1,2-diaminoethane.

Scheme II



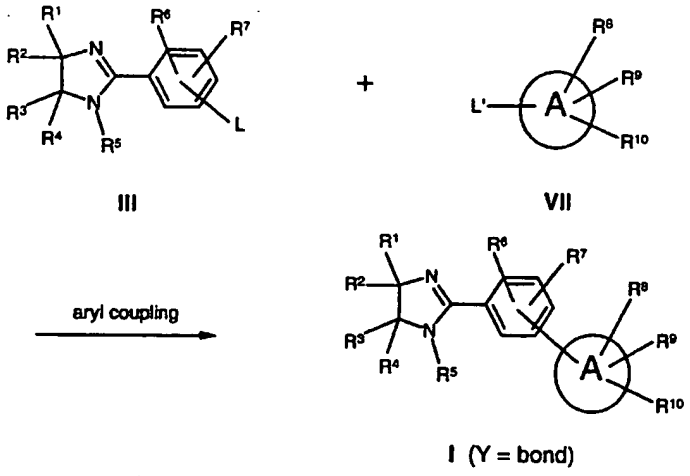
Cyclisation is induced by a silylating agent or a mixture of silylating agents, optionally in the presence of a soluble or insoluble base, e.g. triethylamine or dimethylaminomethyl polystyrene and a solvent. Useful reagents are e.g. described in FLUKA Chemika, "Silylating Agents" (1995) ISBN 3-905617-08-0 and the literature cited therein.

In a more preferred embodiment, these silylating agents are trimethylsilyl halides, TMS-X (e.g. trimethylsilyl chloride or trimethylsilyl iodide) or hexamethyl disilazane, HMDS or trimethylsilyl diethylamine, TMS-DEA or mixtures of them. In the most preferred embodiment the reactions are carried out either in dichloromethane with an excess TMS-Cl or, more preferred, TMS-I in presence of triethylamine or dimethylaminomethyl polystyrene at ambient temperature, or in neat HMDS or a

mixture of HMDS / TMS-Cl 100:1, without additional base and solvent at 50°C to reflux, preferably at 70°C to 90°C. In some cases, using TMS-X as cyclizing reagent, excessive reagent has to be added in several portions within a period of time (up to about a week) to ensure complete conversion. The process described herein is compatible to many functionalities present in an organic molecule, e.g. unprotected hydroxy, unprotected amino, olefinic double bond, cyano, nitro, aromatic halogen, amide, and it is successful in some cases, when conventional methods fail (Chem. Pharm. Bull. **1980, 28**, 1394-1402).

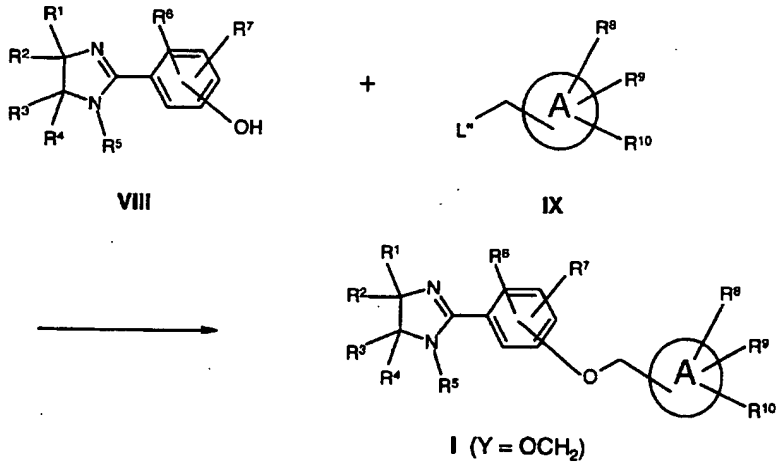
The process described in Scheme II affords numerous advantages over similar methods known in the art. The transformation can be achieved in high yield and under mild conditions, whereas, methods known in the art require the use of extreme conditions or reagents.

Scheme III



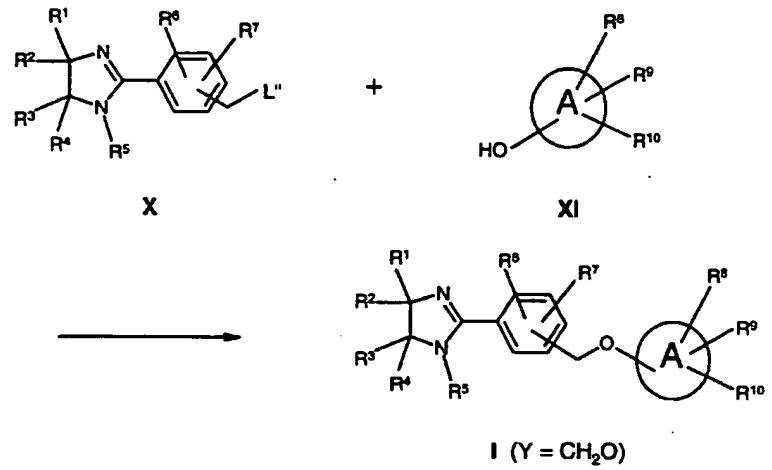
Scheme III describes the synthesis of compounds of Formula I in which the group Y is a bond from intermediates of Formula III and Formula VII by an aryl coupling reaction. Such aryl couplings are any appropriate method for coupling two aromatic or heteroaromatic rings known to the artisan. These may include, but are not limited to Ullmann, Stille, or Suzuki coupling methods. The Suzuki coupling is an especially preferred coupling method using intermediates of Formula III in which the leaving group L is selected from bromo, iodo, or fluoro C_{1-4} alkylsulfonyloxy, more preferred bromo, and intermediates of Formula VII in which L' is $B(OH)_2$. The Suzuki method is catalysed by a Pd catalyst. The artisan will appreciate that there are a variety of available Pd catalysts which are acceptable. One such Pd catalyst which is preferred for the methods described herein is $Pd(PPh_3)_4$.

Scheme IV



I (Y = OCH_2)

Scheme V

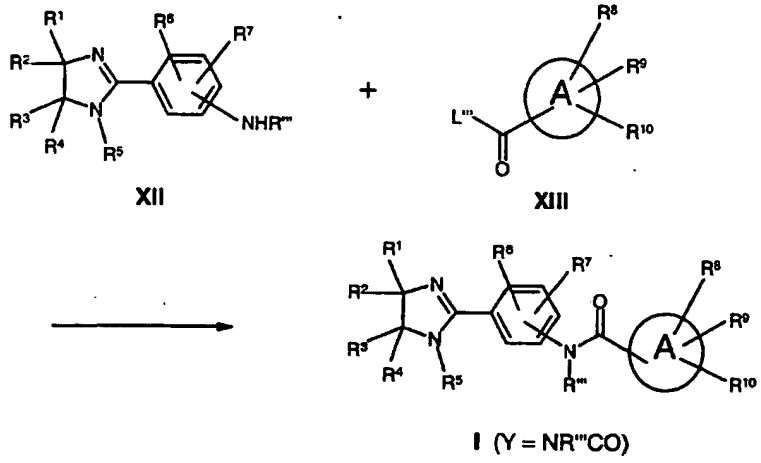


X XI

I (Y = CH_2O)

Schemes IV and V describe the synthesis of compounds of Formula I in which the group Y is OCH_2 or CH_2O, respectively. The compounds may be prepared by alkylation of (hetero)aromatic hydroxycompounds of Formula VIII or Formula XI with compounds of Formula IX or Formula X, respectively, which contain a leaving group L'', preferably a halo group, more preferred bromo or chloro. The skilled artisan will appreciate that there are a large number of methods available for such a transformation. In a preferred method the reactants are heated in an inert solvent like acetone or butanone in the presence of a base like potassium carbonate.

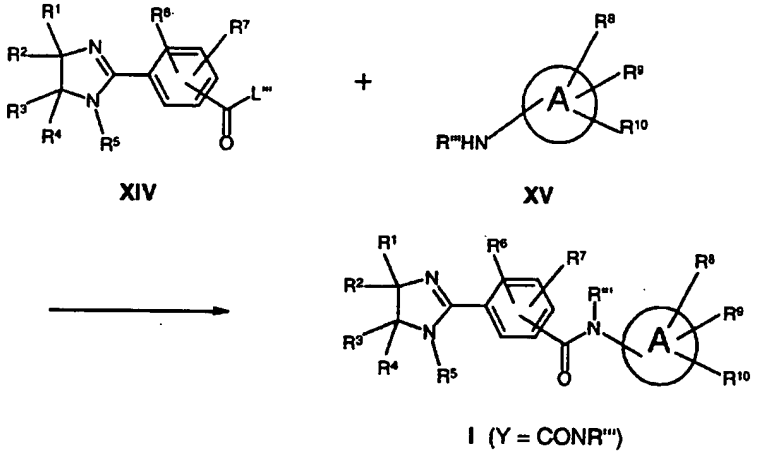
Scheme VI



XII XIII

I (Y = NR'''CO)

Scheme VII



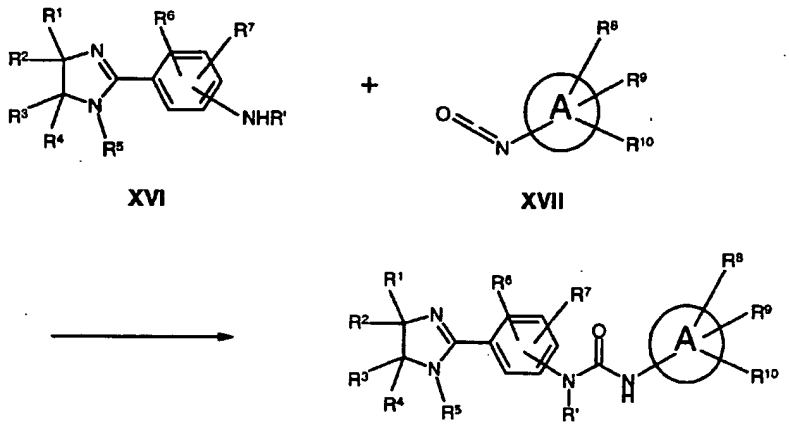
XIV XV

I (Y = CONR''')

Schemes VI and VII describe the synthesis of compounds of Formula I in which the group Y is an amide group NR'''CO or CONR''', respectively, and R''' is

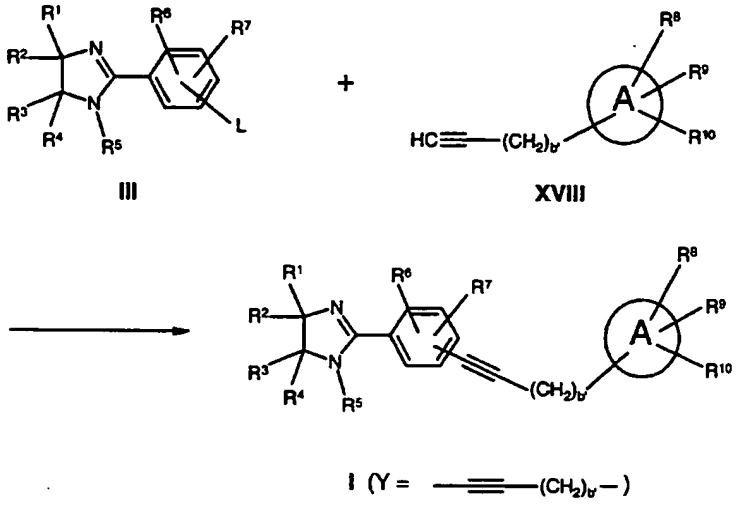
selected from the group consisting of hydrogen, C_{1-4} alkyl, and benzyl. The compounds are prepared by standard methods for formation of such an amide bond which are well known to those skilled in the art using (hetero)aromatic amines of Formula **XII** or Formula **XV** and derivatives of (hetero)aromatic carboxylic acids of Formula **XIII** or Formula **XIV**. The group L''' in those carboxylic acid derivatives may be a hydroxy group, a halo group, preferably chloro, representing acid chlorides of Formula **XIII** or Formula **XIV** (L''' = Cl), or any other leaving group known from the art which activates a carboxylic acid for such a condensation reaction.

Scheme VIII



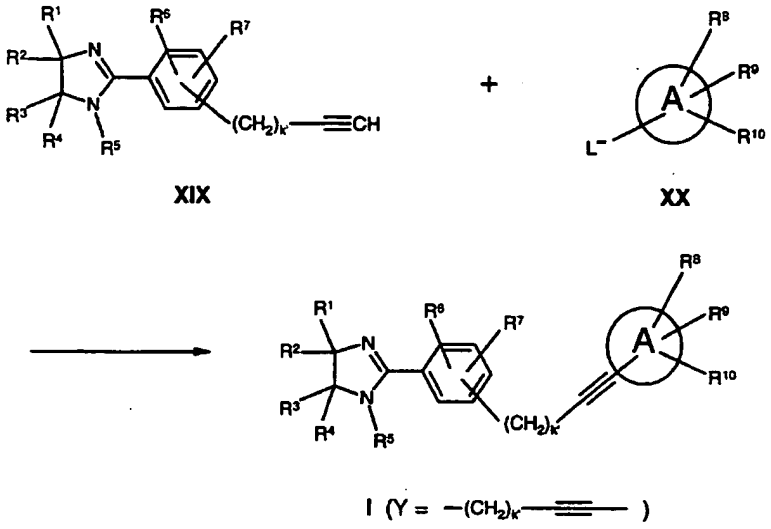
Scheme VIII describes the synthesis of compounds of Formula **I** in which the group Y is a group NR'CONH wherein R' is selected from the group consisting of hydrogen, C_{1-4} alkyl, and benzyl. The compounds may be prepared by addition of aromatic amines of Formula **XVI** to (hetero)aromatic isocyanates of Formula **XVII** which can be carried out by standard methods which are well known to the skilled artisan.

Scheme IX



Scheme IX describes the synthesis of compounds of Formula I in which Y is a group -C≡C-$(CH_2)_{b'}$-, in which b' is a number selected from 0, 1, 2, or 3. The compounds may be prepared by reaction of intermediates of Formula III with terminal alkynes of Formula XVIII. The skilled artisan appreciates that a number of methods for this reaction is known in the art. Preferred leaving groups L in compounds of Formula III are bromo or iodo. The reaction is carried out in the presence of a Pd catalyst like $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2(PPh_3)_2$, a Cu(I) halide like CuI, and in the presence of a base, preferably in an organic amino compound like triethylamine, diisopropylamine, tributylamine, propylamine, butylamine, diethylamine, piperidine, pyrrolidine or a mixture of such an amine with an inert solvent like DMF. The reaction may be carried out at ambient or elevated temperature up to reflux of the mixture. In a preferred method, a mixture of an aryl halide of Formula III (L = Br, I), an alkyne of Formula XVIII, and triethylamine is heated at 50 – 90 °C in the presence of Cu(I) iodide and $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$.

Scheme X



XIX XX

I (Y = $-(CH_2)_{k'}-C\equiv C-$)

Scheme X describes the synthesis of compounds of Formula I in which Y is a group $-(CH_2)_{k'}-C\equiv C-$ and k' is a number selected from 0, 1, 2, or 3. The reaction is carried out under the same conditions as described for Scheme IX starting from alkynes of Formula XIX and aromatic halides of Formula XX. Preferred leaving groups

By virtue of their acidic moieties, some of the compounds of Formula I include the pharmaceutically acceptable base addition salts thereof. Such salts include those derived from inorganic bases such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium

bicarbonate, calcium hydroxide, methylamine, diethylamine, ethylenediamine, cyclohexylamine, ethanolamine and the like.

Because of a basic moiety, some of the compounds of Formula I can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para- bromophenylsulfonic, carbonic, succinic, citric, benzoic, acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, mono-hydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, 2-butyne-1,4 dioate, 3-hexyne-2, 5-dioate, benzoate, chlorobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, hippurate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-l-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts.

In addition, it is recognised that compounds of the present invention may form a variety of solvates with a number of different solvents. Representative solvates can be useful as final embodiments of the present invention or as intermediates in the isolation or preparation of the final embodiments of this invention. For example solvates can be prepared with lower alcohols such as ethanol and with alkyl esters such ethylacetate.

It is recognised that various stereoisomeric forms of the compounds of Formula I may exist. The compounds may be prepared as racemates and can be conveniently used as such. Therefore, the racemates, individual enantiomers (including, but in no-way limited to atropisomers), diastereomers, or mixtures thereof form part of the present invention. Unless otherwise specified, whenever a compound is described or referenced in this specification all the racemates, individual

enantiomers, diastereomers, or mixtures thereof are included in said reference or description.

In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

The artisan appreciates that, in some instances, desired isomeric forms may be obtained using separation methods which are generally known.

Compounds of Formula (I) have primary action during hyperglycemia in that they improve glucose tolerance without producing marked reduction in basal plasma glucose levels.

Compounds of the invention were active in screens for activity using assays based on the use of BTC6 cells, for example as described by Poitout,V et al. Diabetes 44:306-313 (1995) and D'Ambra ,R et al Endocrinology, 126: 2815-2822 (1990)] and rat Langerhans islets, for example as described by Lacy, P.E and Kostianovsky,M. Diabetes (1967),and as described in more detail in hereinbelow, and in an Intravenous Glucose Tolerance Test as described hereinbelow.

The invention further includes a method of treating diabetes in which an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or ester thereof is administered to a patient requiring such treatment.

Preparations and Examples

The following examples and preparations are provided merely to further illustrate the invention. The scope of the invention is not in any way limited or to be construed as merely consisting of the following examples. In the following examples and preparations, melting point, nuclear magnetic resonance spectra, mass spectra, high pressure liquid chromatography over silica gel, gas chromatography, N,N-

dimethylformamide, palladium on charcoal, tetrahydrofuran, ethyl acetate, thin layer chromatography and elemental analysis are abbreviated M.Pt. or m.p., NMR, MS, HPLC, GC, DMF, Pd/C, THF, EtOAc, TLC and EA respectively. The terms "EA", "TLC", "NMR", and "MS", when being utilised in the preparations, indicate that the data indicated was consistent with the desired structure. Reported melting points are uncorrected and yields are not optimised.

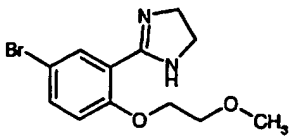
Intermediate 1: Ethyl 5-Bromo-2-(2-methoxyethoxy)benzoate

To a solution of 20 g (81.6 mmol) of ethyl 5-bromo-2-hydroxybenzoate (prepared by the procedure from J.Chem.Soc., Perkin Trans. I, 1977, 1647) in 200 ml DMF were added 11.28 g (81.6 mmol) potassium carbonate and 13.9 g (100 mmol) 2-methoxyethyl bromide. The mixture was heated at 80 °C for 48 hours. After cooling to room temperature it was poured into water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 22.8 g (89%) of the title compound as a syrup.

Intermediate 2: 2-Aminoethyl 5-Bromo-2-(2-methoxyethoxy)benzamide

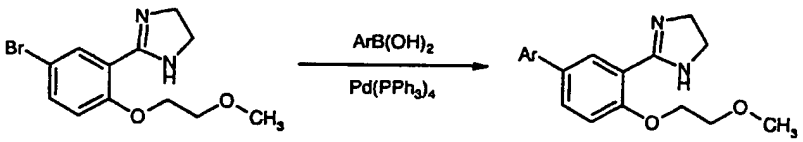
A mixture of 22.6 g (74.5 mmol) of Intermediate 1 and 44 g (745 mmol) 1,2-diaminoethane was heated for 8 hours at 100 °C. After cooling to room temperature water (500 ml) was added. The precipitate was collected by filtration, washed with water, and dried to give 19 g (80 %) of the amorphous title compound.

Intermediate 3: 2-[5-Bromo-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole



To 18.8 g (59.2 mmol) of Intermediate 2 was carefully added $POCl_3$. The mixture was heated for 8 hours at 80-90 °C. After evaporation it was poured into ice-water, made basic with 5 N NaOH, and extracted with dichloromethane. The extract was washed with water, dried, and concentrated *in vacuo*. The title imidazoline was purified by chromatography with dichloromethane / ethanol 7:3 on silica gel.
Yield: 10 g (56 %); beige amorphous solid; m.p. 182 °C (dec.)

The following Examples 1 - 24 of the present invention were prepared by Suzuki coupling with arylboronic acids as described for Example 1:



Examples 1 - 24

Example 1: 2-(3'-Chloro-4'-fluoro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-chloro-4-fluorophenyl)

To a solution of 0.4 g (1.3 mmol) of Intermediate 3 in 20 ml 1,4-dioxane were added under argon 115 mg (0.1 mmol) $Pd(PPh_3)_4$ and 2 ml 2M aqueous Na_2CO_3. After addition of 244 mg (1.5 mmol) (3-chloro-4-fluorobenzene)boronic acid the mixture was heated for 18 hours at 80 °C. It was cooled to room temperature, the solid removed by filtration and the solution acidified with 2N HCl. After concentration *in*

vacuo it was chromatographed on silica gel with dichloromethane / ethanol 9:1 to give 0.16 g (36 %) of the title compound as a beige crystalline solid; m.p. 204-206 °C.

Example 2: 2-[5-(5-Chloro-2-thienyl)-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 5-chloro-2-thienyl)

Yield: 13 %; beige amorphous solid; MS 336 (M^+)

Example 3: 2-(4-(2-Methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = phenyl)

Yield: 24 %; beige amorphous solid; MS 296 (M^+)

Example 4: 2-(3',5'-Bistrifluoromethyl-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 3,5-bistrifluoromethylphenyl)

Yield: 23 %; beige amorphous solid; MS 432 (M^+)

Example 5: 2-[2-(2-Methoxyethoxy)-5-(3-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-thienyl)

Yield: 30 %; beige solid; m.p. 226 °C; MS 302 (M^+)

Example 6: 2-[2-(2-Methoxyethoxy)-5-(2-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-thienyl)

Yield: 50 %; beige amorphous solid; MS 302 (M^+)

Example 7: 2-(4'-Chloro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-chlorophenyl)

Yield: 28 %; beige amorphous solid; MS 330 (M^+)

Example 8: 2-[2-(2-Methoxyethoxy)-5-(2-naphthyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-naphthyl)

Yield: 18 %; brown amorphous solid; MS 346 (M^+)

Example 9: 2-(4-(2-Methoxyethoxy)-4'-trifluoromethyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-trifluoromethylphenyl)

Yield: 24 %; beige amorphous solid; MS 364 (M^+)

Example 10: 2-(3',5'-Dichloro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3,5-dichlorophenyl)

Yield: 18 %; beige amorphous solid; MS 364 (M^+)

Example 11: 2-(4-(2-Methoxyethoxy)-3'-trifluoromethyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-trifluoromethylphenyl)

Yield: 21 %; beige solid; m.p. 171-173 °C; MS 364 (M^+)

Example 12: 2-(4'-Fluoro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-fluorophenyl)

Yield: 38 %; beige solid; m.p. 234-235 °C; MS 314 (M^+)

Example 13: 2-(4'-Methoxy-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methoxyphenyl)

Yield: 33 %; beige solid; m.p. 208-209 °C; MS 326 (M^+)

Example 14: 2-(4-(2-Methoxyethoxy)-3'-nitro-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-nitrophenyl)

Yield: 20 %; beige solid; m.p. 184-186 °C; MS 341 (M^+)

Example 15: 2-(4-(2-Methoxyethoxy)-4'-methyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methylphenyl)

Yield: 26 %; beige amorphous solid; MS 310 (M^+)

Example 16: 2-(2',4'-Dichloro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2,4-dichlorophenyl)

Yield: 37 %; beige amorphous solid; MS 364 (M^+)

Example 17: 2-(2'-Methoxy-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-methoxyphenyl)

Yield: 30 %; beige amorphous solid; MS 326 (M^+)

Example 18: 2-(3'-Methoxy-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-methoxyphenyl)

Yield: 14 %; beige amorphous solid; MS 326 (M^+)

Example 19: 2-(4-(2-Methoxyethoxy)-2'-trifluoromethyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-trifluoromethylphenyl)

Yield: 22 %; beige amorphous solid; MS 364 (M^+)

Example 20: 2-(4-(2-Methoxyethoxy)-2'-methyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-methylphenyl)

Yield: 13 %; beige amorphous solid; MS 310 (M^+)

Example 21: 2-(3'-Fluoro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-fluorophenyl)

Yield: 23 %; beige amorphous solid; MS 314 (M^+)

Example 22: 2-(2',4'-Dimethoxy-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2,4-dimethoxyphenyl)

Colorless crystals; m.p. 170-172 °C

Example 23: 2-(3',4'-Dimethoxy-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3,4-dimethoxyphenyl)

Colorless crystals; m.p. 191-193 °C

Example 24: 2-(2',3'-Dichloro-4-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2,3-dichlorophenyl)

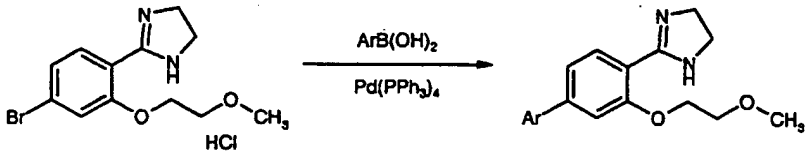
Beige crystalline solid; m.p. 173-175 °C

Intermediate 4: 2-[4-Bromo-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride

The imidazoline was prepared in the same manner as described for Intermediate 3 starting from ethyl 4-bromo-2-hydroxybenzoate;

Colorless crystals; m.p. 174-176 °C

The following Examples 25 - 34 were prepared by Suzuki coupling with arylboronic acids from Intermediate 4 by the procedure described for Example 1:



Intermediate 4 Examples 25 - 34

Example 25: 2-(3-(2-Methoxyethoxy)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = phenyl)

Yield: 50 %; beige crystalline solid; m.p. 202-204 °C; MS 296 (M^+)

Example 26: 2-(3-(2-Methoxyethoxy)-4'-methyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methylphenyl)

Yield: 42 %; beige crystalline solid; m.p. 198-200 °C; MS 310 (M^+)

Example 27: 2-(3-(2-Methoxyethoxy)-3'-trifluoromethyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-trifluoromethylphenyl)

Yield: 37 %; amorphous solid; MS 364 (M^+)

Example 28: 2-(3-(2-Methoxyethoxy)-4'-trifluoromethyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-trifluoromethylphenyl)

Yield: 25 %; amorphous solid; MS 364 (M^+)

Example 29: 2-(4'-Fluoro-3-(2-methoxyethoxy)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-fluorophenyl)

Yield: 68 %; beige crystalline solid; m.p. 190-192 °C; MS 314 (M^+)

Example 30: 2-(3',5'-Dichloro-3-(2-methoxyethoxy)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3,5-dichlorophenyl)

Yield: 8 %; beige crystalline solid; m.p. 210-212 °C; MS 364 (M^+)

Example 31: 2-(4'-Methoxy-3-(2-methoxyethoxy)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methoxyphenyl)

Yield: 62 %; beige crystalline solid; m.p. 202-204 °C; MS 326 (M^+)

Example 32: 2-(3-(2-Methoxyethoxy)-3'-nitro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-nitrophenyl)

Yield: 26 %; beige amorphous solid; MS 341 (M^+)

Example 33: 2-[4-(5-Chloro-2-thienyl)-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 5-chloro-2-thienyl)

Yield: 7 %; yellow amorphous solid; MS 336 (M^+)

Example 34: 2-[2-(2-Methoxyethoxy)-4-(2-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-thienyl)

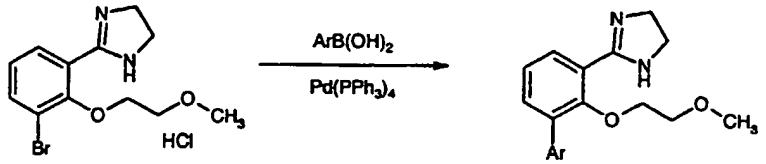
Yield: 57 %; beige crystalline solid; m.p. 210-212 °C; MS 302 (M^+)

Intermediate 5: 2-[3-Bromo-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-

imidazole Hydrochloride

The compound was prepared in the same manner as described for Intermediate 3 starting from ethyl 3-bromo-2-hydroxybenzoate;
beige crystalline solid; m.p. 123-125 °C

The following Examples 35 - 44 were prepared by Suzuki coupling with arylboronic acids from Intermediate 5 by the procedure described for Example 1:



Intermediate 5 Examples 35 - 44

Example 35: 2-[3-(5-Chloro-2-thienyl)-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 5-chloro-2-thienyl)
Yield: 22 %; yellow crystals; m.p. 185-187 °C; MS 336 (M^+)

Example 36: 2-[2-(2-Methoxyethoxy)-3-(2-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-thienyl)
Yield: 10 %; grey crystalline solid; m.p. 189 °C; MS 302 (M^+)

Example 37: 2-[2-(2-Methoxyethoxy)-3-(2-naphthyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-naphthyl)
Yield: 22 %; m.p. 67-69 °C; MS 346 (M^+)

Example 38: 2-[2-(2-Methoxyethoxy)-3-(1-naphthyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 1-naphthyl)

Yield: 22 %; beige crystalline solid; m.p. 124-126 °C; MS 346 (M^+)

Example 39: 2-(2-(2-Methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = phenyl)

Beige crystalline solid; m.p. 181-182 °C; MS 296 (M^+)

Example 40: 2-(4'-Methoxy-2-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methoxyphenyl)

Yield: 9 %; yellow crystals; m.p. 162-164 °C; MS 326 (M^+)

Example 41: 2-(4'-Fluoro-2-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-fluorophenyl)

Yield: 24 %; colorless crystals; m.p. 213-215 °C; MS 314 (M^+)

Example 42: 2-(2-(2-Methoxyethoxy)-4'-methyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methylphenyl)

Yield: 15 %; pale yellow crystals; m.p. 206-207 °C; MS 310 (M^+)

Example 43: 2-(3',5'-Dichloro-2-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3,5-dichlorophenyl)

Yield: 25 %; grey crystalline solid; m.p. 174 °C (dec.); MS 364 (M^+)

Example 44: 2-(4'-Chloro-2-(2-methoxyethoxy)-[1,1'-biphenyl]-3-yl)-4,5-dihydro-

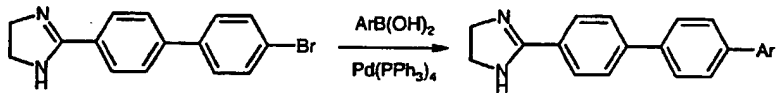
1H-imidazole Hydrochloride (Ar = 4-chlorophenyl)

Yield: 46 %; pale yellow crystals; m.p. 236-238 °C (dec.); MS 330 (M^+)

Example 45: **2-(4'-Bromo-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole**

The title imidazoline was obtained as a brown amorphous solid starting from (4'-bromo-[1,1'-biphenyl]-4-yl)carboxylic acid (prepared according to WO 88/07518) as described for the synthesis of the imidazoline of Intermediate 3.

The following Examples 46 - 56 were prepared by Suzuki coupling with arylboronic acids from Example 45 in the same manner as described for Example 1:



Example 45 Examples 46 - 56

Example 46: 2-(4''-Chloro-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-chlorophenyl)

Example 47: 2-([1,1';4',1'']Terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = phenyl)

Example 48: 2-(4''-Methyl-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methylphenyl)

Example 49: 2-(4''-Fluoro-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-fluorophenyl)

Example 50: 2-(3''-Nitro-[1,1';4',1''terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-nitrophenyl)

Example 51: 2-(3'',5''-Bistrifluoromethyl-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole (Ar = 3,5-bistrifluoromethylphenyl)

Example 52: 2-(4''-Trifluoromethyl-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-trifluoromethylphenyl)

Example 53: 2-(2''-Methoxy-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-methoxyphenyl)

Example 54: 2-(2'',4'',6''-Trimethyl-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2,4,6-trimethylphenyl)

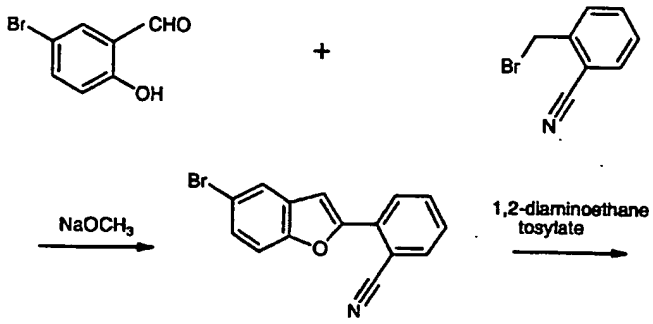
Example 55: 2-(3'',5''-Dichloro-[1,1';4',1'']terphenyl-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3,5-dichlorophenyl)

Example 56: 2-[4'-(5-Chloro-2-thienyl)-[1,1'biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 5-chloro-2-thienyl)

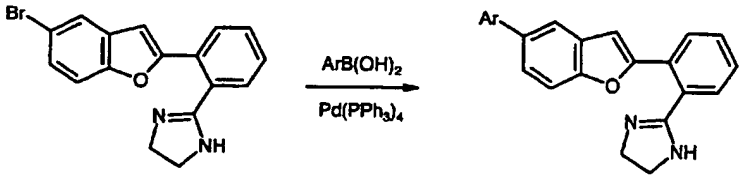
Intermediate 6: 2-(5-Bromobenzofuran-2-yl)benzonitrile

1.88 g (34.7 mmol) sodium methoxide in 6 ml ethanol were added at room temperature to a solution of 6.47 g (32.2 mmol) 5-bromo-2-hydroxybenzaldehyde and 6.31 g (32.2 mmol) 2-cyanobenzyl bromide in DMF (28 ml). After stirring for 8 hours another 1.88 g (34.7 mmol) sodium methoxide in 6 ml ethanol were added followed by heating and stirring at 70 °C for 3 hours. It was cooled to room temperature and the solvents were removed under reduced pressure. Water and dichloromethane were added and the organic layer was separated, dried, and concentrated *in vacuo*. The crystalline title nitrile which had been formed after additon of ethanol was collected by filtration and dried.

Yield: 2.3 g (25 %); m.p. 140 °C



Intermediate 6



Example 57 Examples 58 - 80

Example 57: 2-[2-(5-Bromobenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole

A mixture of 1 g (3.3 mmol) of Intermediate 6 and 0.9 g (3.8 mmol) of 1,2-diaminoethane monotosylate was heated at 210 °C for 5 hours. After cooling to room temperature water (30 ml) and 2N NaOH (30 ml) were added, and the mixture was extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to leave the title imidazoline.

Yield : 0.3 g (26 %); yellow oil

Example 58: 2-[2-(5-(4-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 4-methoxyphenyl)

To a solution of 0.322 g (0.94 mmol) the imidazoline of Example 57 in 1,4-dioxane (15 ml) was added under argon 0.109 g (0.94 mmol) $Pd(PPh_3)_4$ followed by 2 ml 2M aqueous sodium carbonate. After addition of 0.172 g (1.1 mmol) (4-methoxybenzene)boronic acid the mixture was heated for 16 hours at 80 °C. It was cooled to room temperature, the solid removed by filtration, and the solution acidified with 2N HCl. After concentration *in vacuo* the title compound was obtained by chromatography on silica gel with isopropanol / ethyl acetate / methanol / ammonia in ethanol 40:40:5:10.

Yield: 0.27 g (78 %); yellow amorphous solid

The following Examples 59 - 80 were prepared in substantial accordance with the method described for Example 58:

Example 59: 2-[2-(5-(4-Chlorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 4-chlorophenyl)

Yield: 69 %; yellow amorphous solid; MS 372 (M^+)

Example 60: 2-[2-(5-Phenylbenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = phenyl)

Yield: 70%; yellow oil; MS 338 (M^+)

Example 61: 2-[2-(5-(4-Methylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 4-methylphenyl)

Yellow amorphous solid

Example 62: 2-[2-(5-(4-Fluorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-

imidazole (Ar = 4-fluorophenyl)

Yield: 54 %; yellow amorphous solid; MS 356 (M^+)

Example 63: 2-[2-(5-(3-Trifluoromethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-trifluoromethylphenyl)

Yellow amorphous solid

Example 64: 2-[2-(5-(4-Trifluoromethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-trifluoromethylphenyl)

Yield: 35 %; yellow crystalline solid; m.p. > 280 °C; MS 406 (M^+)

Example 65: 2-[2-(5-(3,5-Dichlorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3,5-dichlorophenyl)

Yield: 81 %; yellow crystals; m.p. 273-274 °C; MS 407 (M^+)

Example 66: 2-[2-(5-(3,5-Bistrifluoromethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3,5-bistrifluoromethylphenyl)

Yield: 59 %; colorless crystals; m.p. > 280 °C; MS 474 (M^+)

Example 67: 2-[2-(5-(2,4-Dichlorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2,4-dichlorophenyl)

Yield: 58 %; yellow amorphous solid; MS 407 (M^+)

Example 68: N-(3-(2-[2-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]benzofuran-5-yl)phenyl) acetamide (Ar = 3-($NHCOCH_3$)phenyl)

Yield: 38 %; yellow amorphous solid; MS 395 (M^+)

Example 69: 2-[2-(5-(5-Chloro-2-thienyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 5-chloro-2-thienyl)

Yield: 71 %; yellow amorphous solid; MS 378 (M^+)

Example 70: 2-[2-(5-(3-Nitrophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-nitrophenyl)

Yield: 45 %; yellow amorphous solid; MS 383 (M^+)

Example 71: 2-[2-(5-(4-Methylthiophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 4-(SCH_3)phenyl)

Yield: 34 %; colorless crystals; m.p. 180-182 °C; MS 384 (M^+)

Example 72: 2-[2-(5-(3-Aminophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-aminophenyl)

Yield: 55 %; colorless amorphous solid; MS 353 (M^+)

Example 73: 2-[2-(5-(2-Thienyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-thienyl)

Yield: 52 %; yellow amorphous solid; MS 344 (M^+)

Example 74: 2-[2-(5-(3-Thienyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-thienyl)

Yield: 52 %; yellow crystals; m.p. 290 °C (dec.); MS 344 (M^+)

Example 75: 2-[2-(5-(3-Fluorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-fluorophenyl)

Yield: 46 %; colorless crystals; m.p. 298-299 °C; MS 356 (M^+)

Example 76: 2-[2-(5-(2,4,6-Trimethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2,4,6-trimethylphenyl)

Yield: 19 %; yellow amorphous solid; MS 380 (M^+)

Example 77: 2-[2-(5-(3-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-methoxyphenyl)

Yield: 49 %; yellow amorphous solid; MS 368 (M^+)

Example 78: 2-[2-(5-(2-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-methoxyphenyl)

Yield: 40 %; yellow amorphous solid; MS 368 (M^+)

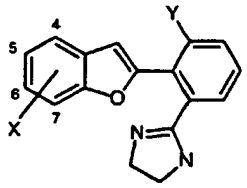
Example 79: 2-[2-(5-(1-Naphthyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 1-naphthyl)

Yield: 88 %; yellow amorphous solid; MS 388 (M^+)

Example 80: 2-[2-(5-(2-Naphthyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-naphthyl)

Yield: 75 %; yellow amorphous solid; MS 388 (M^+)

The following Examples 81 – 91 were prepared in the same manner from the corresponding salicylaldehydes and 2-cyanobenzyl bromides as described for the imidazoline of Example 57. The starting salicylaldehydes were either commercially available or they were synthesized according procedures which are described in the literature.



Examples 81 - 91

Example 81: 2-[2-(Benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (X = H, Y = H)

Prepared from salicylaldehyde and 2-cyanobenzyl bromide;

pale yellow crystals; m.p. > 280 °C

Example 82: 2-[2-(5-Chlorobenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (X = 5-Cl, Y = H)

Prepared from 5-chlorosalicylaldehyde and 2-cyanobenzyl bromide;

brown amorphous solid

Example 83: 2-[2-(Benzofuran-2-yl)-3-chlorophenyl]-4,5-dihydro-1H-imidazole (X = H, Y = Cl)

Prepared from salicylaldehyde and 6-chloro-2-cyanobenzyl bromide;

yellow amorphous solid

Example 84: 2-[2-(6-Methoxybenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = 6-OCH_3, Y = H)

Prepared from 4-methoxysalicylaldehyde and 2-cyanobenzyl bromide;
colorless crystals; m.p. 287 °C

Example 85: 2-[2-(7-Methoxybenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (X = 7-OCH_3, Y = H)

Prepared from 3-methoxysalicylaldehyde and 2-cyanobenzyl bromide;
beige crystalline solid; m.p. 138-142 °C

Example 86: 2-[2-(5-Methoxybenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = 5-OCH_3, Y = H)

Prepared from 5-methoxysalicylaldehyde and 2-cyanobenzyl bromide;
beige crystalline solid; m.p. 269-270 °C

Example 87: 2-[2-(4-Bromobenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (X = 4-Br, Y = H)

Prepared from 6-bromosalicylaldehyde (Chem. Pharm. Bull. 17 (1969), 89) and 2-cyanobenzyl bromide;
Yield: 30 %; pale yellow crystals; m.p. 155-156 °C; MS 340 and 342 (M^+)

Example 88: 2-[2-(5,7-Dibromobenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (X = 5,7-Br_2, Y = H)

Prepared from 3,5-dibromosalicylaldehyde and 2-cyanobenzyl bromide;

yellow amorphous solid

Example 89: 2-[2-(7-Bromobenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (X = 7-Br, Y = H)

Prepared from 3-bromosalicylaldehyde (Chem. Pharm. Bull. 41 (1993), 1166) and 2-cyanobenzyl bromide;

Yield: 24 %; brown amorphous solid; MS 340 and 342 (M^+)

Example 90: 2-[2-(5-Bromo-7-methoxybenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = 5-Br-7-OCH_3, Y = H)

Prepared from 5-bromo-3-methoxysalicylaldehyde and 2-cyanobenzyl bromide;

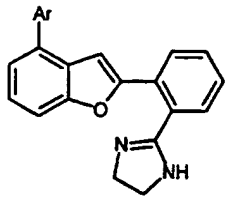
colorless crystals; m.p. 280-281 °C

Example 91: 2-[2-(4-Bromobenzofuran-2-yl)-3-chlorophenyl]-4,5-dihydro-1H-imidazole (X = 4-Br, Y = Cl)

Prepared from 6-bromosalicylaldehyde (Chem. Pharm. Bull. 17 (1969), 89) and 6-chloro-2-cyanobenzyl bromide;

brown resin

The following Examples 92 - 113 were prepared from the imidazoline of Example 87 in substantial accordance with the Suzuki coupling method described for Example 58:



Examples 92 - 113

Example 92: 2-[2-(4-(3-Thienyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-thienyl)

Yield: 79 %; yellow amorphous solid; MS 344 (M^+)

Example 93: 2-[2-(4-(3-Nitrophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-nitrophenyl)

Yield: 78 %; yellow amorphous solid; MS 383 (M^+)

Example 94: 2-[2-(4-(3-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-methoxyphenyl)

Yellow amorphous solid

Example 95: 2-[2-(4-(2-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-methoxyphenyl)

Yellow amorphous solid

Example 96: 2-[2-(4-Phenylbenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = phenyl)

Pale yellow crystals; m.p. 287-289 °C

Example 97: 2-[2-(4-(3-Fluorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochlorid (Ar = 3-fluorophenyl)

Pale yellow crystals; m.p. 297-299 °C

Example 98: 2-[2-(4-(5-Chloro-2-thienyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 5-chloro-2-thienyl)

Yellow crystalline solid; m.p. > 300 °C

Example 99: 2-[2-(4-(2-Thienyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochlorid (Ar = 2-thienyl)

Beige crystalline solid; m.p. 270-272 °C (dec.)

Example 100: 2-[2-(4-(2,4-Dichlorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2,4-dichlorophenyl)

Yellow crystals; m.p. 286-288 °C

Example 101: 2-[2-(4-(4-Fluorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochlorid (Ar = 4-fluorophenyl)

Colorless crystals; m.p. 303-305 °C

Example 102: 2-[2-(4-(3-Trifluoromethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-trifluoromethylphenyl)

Pale yellow crystals; m.p. > 300 °C

Example 103: 2-[2-(4-(4-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methoxyphenyl)

Pale yellow crystals; m.p. 295-296 °C

Example 104: 2-[2-(4-(2,4,6-Trimethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2,4,6-trimethylphenyl)

Yellow crystalline solid; m.p. > 300 °C

Example 105: 2-[2-(4-(3,5-Bistrifluoromethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3,5-bistrifluoromethylphenyl)

Colorless crystals; m.p. 288-290 °C

Example 106: 2-[2-(4-(4-Chlorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-chlorophenyl)

Yellow crystals; m.p. > 300 °C

Example 107: 2-[2-(4-(4-Methylthiophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-(SCH_3)phenyl)

Yellow crystals; m.p. 287-288 °C (dec.)

Example 108: 2-[2-(4-(2-Trifluoromethylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-trifluoromethylphenyl)

Colorless crystals; m.p. > 300 °C

Example 109: 2-[2-(4-(3-Chloro-4-fluorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-chloro-4-fluorophenyl)

Colorless crystals; m.p. > 300 °C

Example 110: 2-[2-(4-(4-Methylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methylphenyl)

Pale yellow crystals; m.p. > 300 °C

Example 111: 2-[2-(4-(2-Methylphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-methylphenyl)

Pale yellow crystals; m.p. 255-258 °C

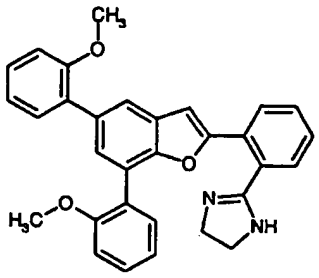
Example 112: 2-[2-(4-(1-Naphthyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 1-naphthyl)

Yellow crystalline solid; m.p. 282-284 °C

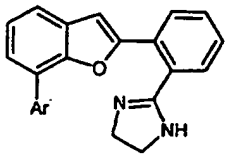
Example 113: 2-[2-(4-(2-Naphthyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-naphthyl)

Yellow crystalline solid; m.p. 288-290 °C

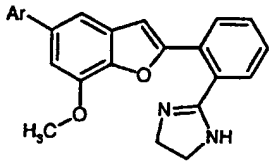
Example 114: 2-[2-(5,7-Bis-(2-methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole



The title compound was prepared from the dibromobenzofuran of Example 88 in the same manner as described for Example 58 using two equivalents (2-methoxybenzene)boronic acid. It was isolated as a yellow amorphous solid.



Examples 115 - 116



Examples 117 - 118

The Examples 115 and 116 and the Examples 117 and 118 were prepared by the Suzuki coupling method from the bromobenzofurans of Examples 89 and 90, respectively, as described before.

Example 115: 2-[2-(7-(3-Fluorophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-fluorophenyl)

Yield: 19 %; colorless crystals; m.p. 215-216 °C; MS 404 (M^+)

Example 116: **2-[2-(7-(2-Methoxyphenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-methoxyphenyl)**

Yield: 30 %; colorless crystals; m.p. 266-267 °C; MS 392 (M^+)

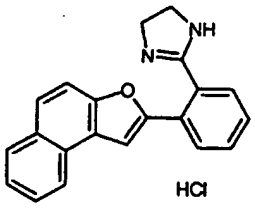
Example 117: **2-[2-(5-(4-Fluorophenyl)-7-methoxybenzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-fluorophenyl)**

Pale yellow crystals; m.p. 288-289 °C

Example 118: **2-[2-(7-Methoxy-5-(3-nitrophenyl)benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-nitrophenyl)**

Yellow crystals; m.p. 260-261 °C

Example 119: **2-[2-(Naphtho[2,1-b]furan-2-yl]phenyl)-4,5-dihydro-1H-imidazole Hydrochloride**

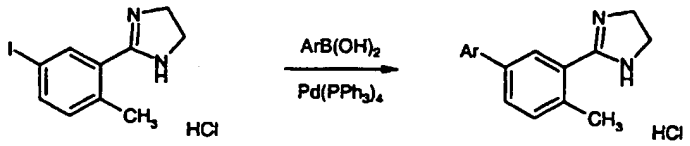


The title compound was prepared from 2-hydroxy-1-naphthaldehyde and 2-cyanobenzyl bromide in the same manner as described for the preparation of Example 57 and obtained as a yellow crystalline solid; m.p. > 300 °C.

Intermediate 7: **2-(5-Iodo-2-methylphenyl)-4,5-dihydro-1H-imidazole**

Hydrochloride

The compound of Intermediate 7 was prepared from 5-iodo-2-methylbenzoic acid (prepared from 5-amino-2-methylbenzoic acid by Sandmeyer reaction) and 1,2-diaminoethane in the same manner as described for the imidazoline of Intermediate 3; colorless crystals; m.p. > 300 °C



Intermediate 7 Examples 120 - 125

The following Examples 120 - 125 were prepared by the Suzuki coupling method as described for Example 1 from the iodobenzene of Intermediate 7.

Example 120: 2-(2'-Methoxy-4-methyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-methoxyphenyl)
Beige crystalline solid; m.p. 212-214 °C

Example 121: 2-[2-Methyl-5-(2-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 2-thienyl)
Beige crystalline solid; m.p. 262-264 °C

Example 122: 2-(3'-Fluoro-4-methyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-fluorophenyl)
Beige crystalline solid; m.p. 218-220 °C

Example 123: 2-[5-(5-Chloro-2-thienyl)-2-methylphenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 5-chloro-2-thienyl)

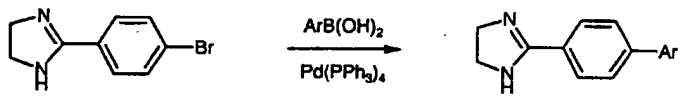
Beige crystalline solid; m.p. 236-238 °C

Example 124: 2-[2-Methyl-5-(3-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 3-thienyl)

Beige crystalline solid; m.p. 252-254 °C

Example 125: 2-(4,4'-Dimethyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride (Ar = 4-methylphenyl)

Beige crystalline solid; m.p. 216-218 °C



Intermediate 8 Examples 126 - 144

The following imidazolines of Examples 126 - 144 are prepared by the Suzuki coupling method as described before from the bromobenzene of Intermediate 8, which was synthesized by using a known procedure from the literature (Heterocycles 47 (1998), 1043).

Example 126: 2-(2',4'-Dichloro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole (Ar = 2,4-dichlorophenyl)

Pale yellow amorphous solid

Example 127: 2-[4-(2-Thienyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-thienyl)
Pale yellow amorphous solid

Example 128: 3-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]pyridine (Ar = 3-pyridinyl)
Pale yellow amorphous solid

Example 129: 2-(3'-Methoxy-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3-methoxyphenyl)
Brown resin

Example 130: 2-(2'-Methoxy-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 2-methoxyphenyl)
Brown amorphous solid

Example 131: 2-(4'-Methylthio-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 4-(SCH_3)phenyl)
Beige amorphous solid

Example 132: 2-[4-(2-Naphthyl)phenyl]-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 2-naphthyl)
Brown amorphous solid

Example 133: 2-[4-(1-Naphthyl)phenyl]-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 1-naphthyl)
Brown resin

Example 134: 2-[4-(5-Chloro-2-thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 5-chloro-2-thienyl)
Brown amorphous solid

Example 135: 2-(3',5'-Bistrifluoromethyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3,5-bistrifluoromethylphenyl)
Beige crystalline solid

Example 136: N-(4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-3-yl)acetamide Hydroiodide (Ar = 3-($NHCOCH_3$)phenyl)
Brown crystalline solid

Example 137: 2-(3'-Amino-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3-aminophenyl)
Brown crystalline solid

Example 138: 2-(3'-Nitro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3-nitrophenyl)
Beige amorphous solid

Example 139: 2-(3'-Trifluoromethyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-

imidazole Hydroiodide (Ar = 3-trifluoromethylphenyl)

Beige amorphous solid

Example 140: 2-(3'-Chloro-4'-fluoro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3-chloro-4-fluorophenyl)

Pale yellow crystalline solid

Example 141: 2-(3'-Fluoro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3-fluorophenyl)

Pale yellow amorphous solid

Example 142: 2-(4'-Fluoro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 4-fluorophenyl)

Pale yellow amorphous solid

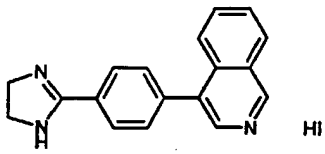
Example 143: 2-(4'-Chloro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 4-chlorophenyl)

Brown amorphous solid

Example 144: 2-[4-(3-Thienyl)phenyl]-4,5-dihydro-1H-imidazole Hydroiodide (Ar = 3-thienyl)

Beige amorphous solid

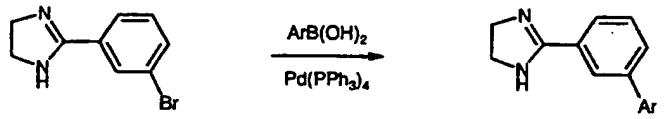
Example 145: 4-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]isoquinoline Hydroiodide



Commercially available 4-bromoisoquinoline and (4-carboxybenzene)boronic acid were coupled by the Suzuki method to give the known intermediate 4-(isoquinolin-4-yl)benzoic acid (WO 98/50358). The carboxylic acid was converted to its 2-aminoethyl amide which was used to prepare the title imidazoline by cyclization with trimethysilyl iodide. It was obtained as a yellow crystalline solid.

Intermediate 9: 2-(3-Bromophenyl)-4,5-dihydro-1H-imidazole

The compound of Intermediate 9 was prepared from 3-bromobenzonitrile in the same manner as its isomer Intermediate 8;
colorless crystals; m.p. 139-140 °C.



Intermediate 9 Examples 146 - 156

Intermediate 9 is used to prepare the compounds of Examples 146-156 by Suzuki coupling as described above.

Example 146: 2-(3'-Fluoro-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 3-fluorophenyl)

Brown amorphous solid

Example 147: 2-(4'-Fluoro-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 4-fluorophenyl)

Brown amorphous solid

Example 148: 2-(2',4'-Dichloro-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 2,4-dichlorophenyl)

Colorless resin

Example 149: 2-(3',5'-Dichloro-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 3,5-dichlorophenyl)

Colorless amorphous solid

Example 150: 2-(2'-Methoxy-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 2-methoxyphenyl)

Brown resin

Example 151: 2-(3'-Methoxy-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 3-methoxyphenyl)

Brown resin

Example 152: 2-(4'-Methylthio-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole (Ar = 4-(SCH_3)phenyl)

Brown resin

Example 153: 2-[3-(2-Thienyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-thienyl)
Pale yellow amorphous solid

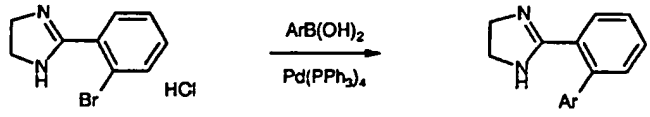
Example 154: 2-[3-(3-Thienyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-thienyl)
Brown amorphous solid

Example 155: 2-[3-(Benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole (Ar = benzofuran-2-yl)
Brown amorphous solid

Example 156: 2-[3-(1-Naphthyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 1-naphthyl)
Brown resin

Intermediate 10: 2-(2-Bromophenyl)-4,5-dihydro-1H-imidazole Hydrochloride

The compound of Intermediate 10 was prepared from 2-bromobenzonitrile in the same manner as described above for its isomers;
colorless crystals; m.p. 267-268 °C.



Intermediate 10 Examples 157 - 174

Intermediate 10 is used to prepare the compounds of Examples 157-174 as described before by the Suzuki coupling method.

Example 157: 2-[2-(1-Naphthyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 1-naphthyl)
Brown resin

Example 158: 2-[2-(3-Thienyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 3-thienyl)
Brown resin

Example 159: 2-(4'-Methylthio-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 4-(SCH_3)phenyl)
Brown resin

Example 160: 2-(2'-Methoxy-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 2-methoxyphenyl)
Brown resin

Example 161: 2-(3',5'-Bistrifluoromethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 3,5-bistrifluoromethylphenyl)
Brown resin

Example 162: 2-(3'-Amino-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 3-aminophenyl)

Brown resin

Example 163: 2-(3'-Fluoro-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 3-fluorophenyl)

Pale yellow amorphous solid

Example 164: 2-(4'-Fluoro-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 4-fluorophenyl)

Yellow viscous oil

Example 165: 2-(4'-Chloro-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 4-chlorophenyl)

Yellow resin

Example 166: 2-(3'-Chloro-4'-fluoro-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 3-chloro-4-fluorophenyl)

Yellow amorphous solid

Example 167: 2-(2',4'-Dichloro-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 2,4-dichlorophenyl)

Yellow amorphous solid

Example 168: 2-(3'-Trifluoromethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 3-trifluoromethylphenyl)

Yellow amorphous solid

Example 169: 2-(4'-Trifluoromethyl-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 4-trifluoromethylphenyl)

Yellow amorphous solid

Example 170: 2-(3'-Methoxy-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 3-methoxyphenyl)

Yellow amorphous solid

Example 171: 2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole (Ar = 4-methoxyphenyl)

Yellow amorphous solid

Example 172: 2-[2-(2-Naphthyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-naphthyl)

Yellow amorphous solid

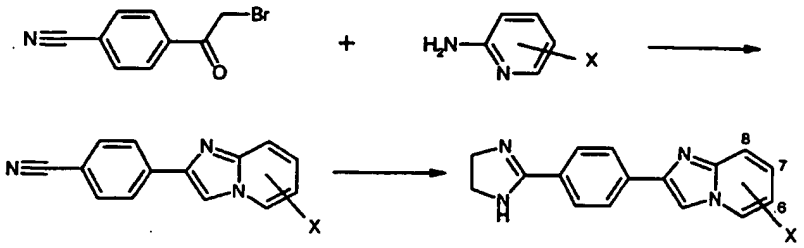
Example 173: 2-[2-(2-Thienyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 2-thienyl)

Yellow resin

Example 174: 2-[2-(5-Chloro-2-thienyl)phenyl]-4,5-dihydro-1H-imidazole (Ar = 5-chloro-2-thienyl)

Yellow resin

4-(Bromoacetyl)benzonitrile was purchased from Lancaster and used to prepare the intermediate 4-(imidazo[1,2-a]pyridin-2-yl)benzonitriles with 2-aminopyridines by standard methods which are known for this condensation reaction. The compounds of Examples 175-179 were prepared from these intermediate nitriles by saturating an ethanolic solution with hydrochloric acid followed by reaction with 1,2-diaminoethane.



Examples 175 - 179

Example 175: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-8-methyl-imidazo[1,2-a]pyridine (X = 8-CH_3)

Beige crystalline solid; m.p. 221-225 °C

Example 176: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-7-methyl-imidazo[1,2-a]pyridine (X = 7-CH_3)

Beige crystalline solid; m.p. 234 °C (dec.)

Example 177: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-methyl-imidazo[1,2-a]pyridine (X = 6-CH_3)

Colorless crystals; m.p. 269 °C (dec.)

Example 178: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-8-phenylmethoxy-imidazo[1,2-a]pyridine (X = 8-benzyloxy)

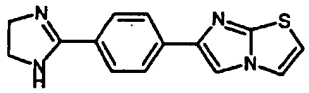
Beige crystalline solid; m.p. 224-227 °C

Example 179: 6-Bromo-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-imidazo[1,2-a]pyridine (X = 6-Br)

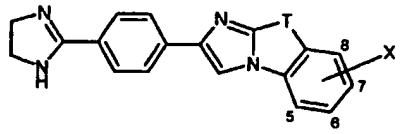
Beige crystalline solid; m.p. > 293 °C

The following Examples 180-188 were prepared in the same manner starting from commercially available 2-aminoazoles:

Example 180: 6-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-imidazo[2,1-b]thiazole



prepared from 2-aminothiazole; beige crystalline solid; m.p. 224-228 °C



Examples 181 - 188

Example 181: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-benzo[d]imidazo[2,1-b]thiazole (T = S, X = H)

prepared from 2-aminobenzothiazole; beige crystalline solid; m.p. 209-212 °C

Example 182: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-9-methyl-9H-imidazo[1,2-a]benzimidazole (T = NCH_3, X = H)

prepared from 2-amino-1-methylbenzimidazole; yellow crystalline solid; m.p. 219-223 °C

Example 183: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-9H-imidazo[1,2-a]benzimidazole (T = NH, X = H)

prepared from 2-aminobenzimidazole; beige crystalline solid; m.p. > 320 °C (dec.)

Example 184: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-5-methoxy-benzo[d]imidazo[2,1-b]thiazole (T = S, X = 5-OCH_3)

prepared from 2-amino-4-methoxybenzothiazole; pale yellow crystalline solid; m.p. 237-239 °C

Example 185: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-7-methoxy-benzo[d]imidazo[2,1-b]thiazole (T = S, X = 7-OCH_3)

prepared from 2-amino-6-methoxybenzothiazole; yellow crystalline solid; m.p. 263-269 °C

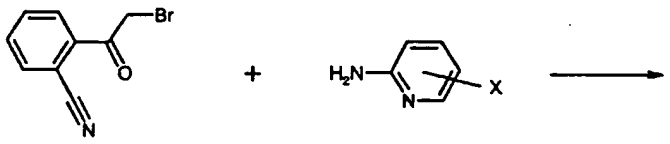
Example 186: 5-Chloro-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-benzo[d]imidazo[2,1-b]thiazole (T = S, X = 5-Cl)

prepared from 2-amino-4-chlorobenzothiazole; beige crystalline solid; m.p. 230-235

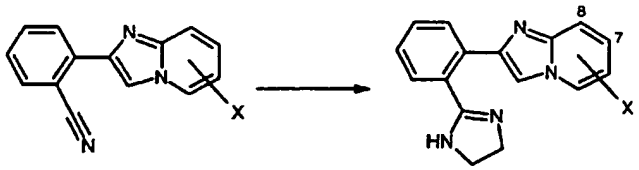
°C

Example 187: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-5-methyl-benzo[d]imidazo[2,1-b]thiazole (T = S, X = 5-CH_3)
prepared from 2-amino-4-methylbenzothiazole; pale yellow crystalline solid; m.p. > 150 °C (dec.)

Example 188: 6-Chloro-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-benzo[d]imidazo[2,1-b]oxazole (T = O, X = 6-Cl)
prepared from 2-amino-5-chlorobenzoxazole; pale yellow crystalline solid; m.p. 250-257 °C (dec.)



Intermediate 11



Examples 189 - 190

2-Cyanoacetophenone was prepared by heating of 2-bromoacetophenone with Cu(I) cyanide in the presence of iodine and converted to its phenacyl bromide (Intermediate 11) using pyrrolidinone hydrotribromide. This intermediate was used to prepare the

compounds of Examples 189-190 as described before, but with the difference that during the condensation reaction to give the imidazo[1,2-a]pyridine nucleus the corresponding primary carboxamides had been formed which were dehydrated to the intermediate 2-(imidazo[1,2-a]pyridin-2-yl)benzonitriles by heating in $POCl_3$.

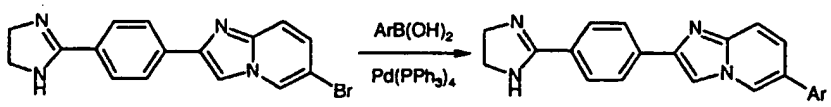
Example 189: 2-[2-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-7-methyl-imidazo[1,2-a]pyridine Hydrochloride (X = 7-CH_3)

Beige crystalline solid; m.p. > 295 °C (dec.)

Example 190: 2-[2-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-8-phenylmethoxy-imidazo[1,2-a]pyridine Hydrochloride (X = 8-benzyloxy)

Beige crystalline solid; m.p. 114-116 °C (dec.)

The imidazoline of Example 179 was used to prepare the compounds of Examples 191-199 by Suzuki coupling methodology as describend before.



Example 179 Examples 191 - 199

Example 191: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-(4-methoxyphenyl)-imidazo[1,2-a]pyridine (Ar = 4-methoxyphenyl)

Beige crystalline solid; m.p. > 298 °C (dec.)

Example 192: 6-(2,4-Dichlorophenyl)-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-imidazo[1,2-a]pyridine (Ar = 2,4-dichlorophenyl)
Beige crystalline solid; m.p. 220 °C (dec.)

Example 193: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-(1-naphthyl)-imidazo[1,2-a]pyridine Hydrochloride (Ar = 1-naphthyl)
Beige crystalline solid; m.p. > 300 °C (dec.)

Example 194: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-(2-methoxyphenyl)-imidazo[1,2-a]pyridine Hydrochloride (Ar = 2-methoxyphenyl)
Yellow crystals; m.p. 313-317 °C (dec.)

Example 195: 6-(Benzofuran-2-yl)-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-imidazo[1,2-a]pyridine Hydrochloride (Ar = 2-benzofuranyl)
Pale yellow crystals; m.p. > 320 °C (dec.)

Example 196: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-(3-thienyl)-imidazo[1,2-a]pyridine (Ar = 3-thienyl)
Beige crystalline solid; m.p. 258-262 °C

Example 197: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-(4-methylphenyl)-imidazo[1,2-a]pyridine (Ar = 4-methylphenyl)
Colorless crystals; m.p. 233-234 °C

Example 198: 2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-phenyl-imidazo[1,2-

a]pyridine (Ar = phenyl)

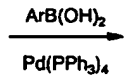
Pale yellow crystals; m.p. 214-216 °C

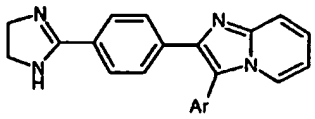
Example 199: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-6-(3-methoxyphenyl)-imidazo[1,2-a]pyridine (Ar = 3-methoxyphenyl)**

Beige crystalline solid; m.p. 115-119 °C

Intermediate 12

Example 200





Examples 201 - 209

4-(3-Bromoimidazo[1,2-a]pyridin-2-yl)benzonitrile (Intermediate 12) was obtained according to a literature procedure (DE 4327027) and used to prepare the imidazoline of Example 200, from which the compounds of the Examples 201-209 were prepared by Suzuki coupling reaction with the corresponding arylboronic acids.

Example 200: **3-Bromo-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-imidazo[1,2-a]pyridine**

Beige amorphous solid; m.p. 198-199 °C

Example 201: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-phenyl-imidazo[1,2-a]pyridine (Ar = phenyl)**

Yellow crystals; m.p. 203 °C

Example 202: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-(2-methoxyphenyl)-imidazo[1,2-a]pyridine (Ar = 2-methoxyphenyl)**

Yellow crystals; m.p. 151 °C (dec.)

Example 203: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-(3-methoxyphenyl)-imidazo[1,2-a]pyridine (Ar = 3-methoxyphenyl)**

Pale yellow crystals; m.p. > 227 °C (dec.)

Example 204: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-(4-methoxyphenyl)-imidazo[1,2-a]pyridine (Ar = 4-methoxyphenyl)**

Pale yellow crystals; m.p. 194-196 °C

Example 205: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-(4-methylphenyl)-imidazo[1,2-a]pyridine (Ar = 4-methylphenyl)**

Yellow crystals; m.p. 174-176 °C

Example 206: **3-(Benzofuran-2-yl)-2-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-imidazo[1,2-a]pyridine Hydrochloride (Ar = 2-benzofuranyl)**

Yellow amorphous solid; m.p. 226-227 °C

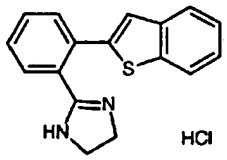
Example 207: **3-(2,4-Dichlorophenyl)-2-[4-(4,5-dihydro-1H-imidazol-2-**

yl)phenyl]-imidazo[1,2-a]pyridine (Ar = 2,4-dichlorophenyl)
Beige crystalline solid; m.p. > 320 °C (dec.)

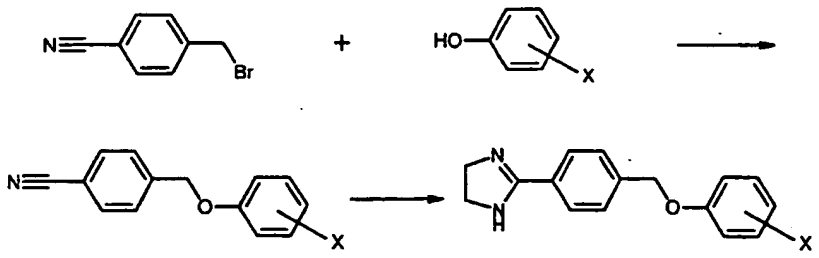
Example 208: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-(1-naphthyl)-imidazo[1,2-a]pyridine (Ar = 1-naphthyl)**
Beige crystalline solid; m.p. 189-192 °C

Example 209: **2-[4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl]-3-(3-thienyl)-imidazo[1,2-a]pyridine (Ar = 3-thienyl)**
Yellow crystals; m.p. 217-220 °C

Example 210: **2-(2-(Benzo[b]thiophen-2-yl)phenyl)-4,5-dihydro-1H-imidazole Hydrochloride**



The title imidazoline was prepared in the same manner as described for the benzofuran of Example 57 starting from 2-mercaptobenzaldehyde (Synthesis 1989, 763);
brown crystalline solid; m.p. 272-274 °C (dec.)



Examples 211 - 213

A mixture of the corresponding methoxyphenol, 4-cyanobenzyl bromide, and potassium carbonate was heated with reflux in acetone to give the intermediate 4-cyanobenzylethers which were used to prepare the imidazolines of Examples 211-213 by heating in neat 1,2-diaminoethane in the presence of a catalytic amount of carbon disulfide.

Example 211: 2-[4-((2-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 2-OCH_3)

Colorless crystals; m.p. 142-144 °C

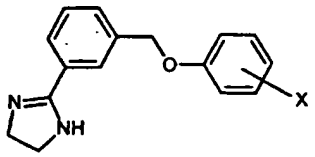
Example 212: 2-[4-((3-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 3-OCH_3)

Colorless crystals; m.p. 123-124 °C

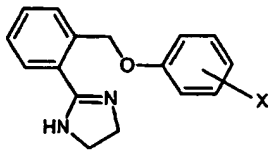
Example 213: 2-[4-((4-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 4-OCH_3)

Colorless crystals; m.p. 153-155 °C

The compounds of the Examples 214-216 and 217-219 were prepared in substantially the same manner starting from 3-cyanobenzyl bromide or 2-cyanobenzyl bromide, respectively.



Examples 214 - 216



Examples 217 - 219

Example 214: 2-[3-((2-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 2-OCH_3)

Colorless crystals; m.p. 92-93 °C

Example 215: 2-[3-((3-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 3-OCH_3)

Colorless viscous oil

Example 216: 2-[3-((4-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 4-OCH_3)

Colorless crystals; m.p. 128-129 °C

Example 217: 2-[2-((2-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 2-OCH_3)

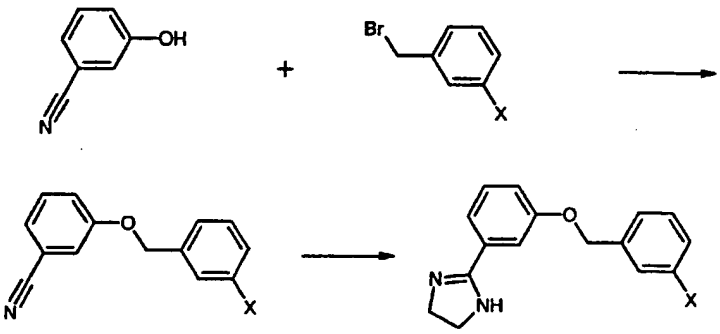
Yellow viscous oil

Example 218: 2-[2-((3-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 3-OCH_3)

Colorless crystalline solid; m.p. 76-77 °C

Example 219: 2-[2-((4-Methoxyphenoxy)methyl)phenyl]-4,5-dihydro-1H-imidazole (X = 4-OCH_3)

Reddish viscous oil



Examples 220 - 221

3-Cyanophenol was alkylated with benzyl bromide or 3-methoxybenzyl bromide, respectively, followed by preparation of the imidazolines of Examples 220 and 221 from the intermediate benzylethers as described above with 1,2-diaminoethane in the presence of carbon disulfide.

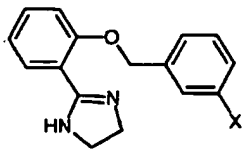
Example 220: **2-[3-(Phenylmethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = H)**

Colorless crystalline solid; m.p. 130-132 °C

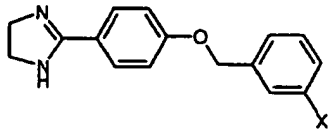
Example 221: **2-[3-((3-Methoxyphenyl)methoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = OCH_3)**

Colorless crystalline solid; m.p. 124-125 °C

The imidazolines of the Examples 222 and 223 and the Examples 224 and 225 were prepared the same manner from 2-cyanophenol and 4-cyanophenol, respectively.



Examples 222 - 223



Examples 224 - 225

Example 222: **2-[2-(Phenylmethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = H)**

Yellow crystalline solid; m.p. 103-105 °C (dec.)

Example 223: **2-[2-((3-Methoxyphenyl)methoxy)phenyl]-4,5-dihydro-1H-imidazole (X = OCH_3)**

Yellow oil

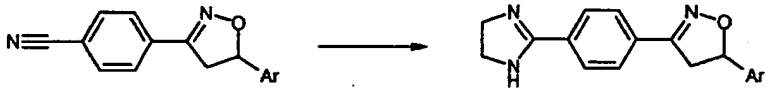
Example 224: 2-[4-(Phenylmethoxy)phenyl]-4,5-dihydro-1H-imidazole (X = H)

Colorless crystalline solid; m.p. 212 °C

Example 225: 2-[4-((3-Methoxyphenyl)methoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = OCH_3)

Colorless crystalline solid; m.p. 219-220 °C

Intermediate 13



Examples 226 - 242

The following Examples 226-242 were prepared by reaction of 4-cyanobenzonitrile oxide with styrene derivatives giving the intermediate 3-(4-cyanophenyl)-4,5-dihydroisoxazoles which were converted to the imidazolines by saturating an ethanolic solution of the nitrile with hydrochloric acid followed by treatment with 1,2-diaminoethane. The nitrile oxide was generated from 4-cyano-N-hydroxybenzenecarboximidoyl chloride (Intermediate 13, prepared according to a procedure from WO 95/14682) with triethylamine in methanol.

Example 226: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-phenyl-4,5-dihydro-isoxazole (Ar = phenyl)
Colorless crystals; m.p. 215-216 °C

Example 227: 5-(4-Aminophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazole (Ar = 4-aminophenyl)
Yellow crystalline solid; m.p. 197-198 °C

Example 228: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(2,4-dimethylphenyl)-4,5-dihydro-isoxazole (Ar = 2,4-dimethylphenyl)
Colorless crystals; m.p. 179 °C

Example 229: 5-([1,1'-Biphenyl]-4-yl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazole (Ar = [1,1'-biphenyl]-4-yl)
Colorless amorphous solid; m.p. 272-275 °C

Example 230: N-[4-(3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazol-5-yl)phenyl] benzamide (Ar = 4-(NHCOphenyl)phenyl)
The intermediate nitrile was prepared by reaction of 4-[5-(4-aminophenyl)-4,5-dihydro-isoxazol-3-yl]benzonitrile (the intermediate used to prepare the imidazoline of Example 227) with benzoyl chloride;
pale amorphous solid; m.p. 277-278 °C

Example 231: 5-(4-Chlorophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazole (Ar = 4-chlorophenyl)
Colorless crystals; m.p. 230-232 °C

Example 232: 5-(2,6-Dichlorophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazole (Ar = 2,6-dichlorophenyl)

Colorless crystals; m.p. 213-214 °C

Example 233: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(2-methylphenyl)-4,5-dihydro-isoxazole (Ar = 2-methylphenyl)

Colorless crystalline solid; m.p. 172-173 °C

Example 234: Ethyl 4-(3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazol-5-yl)benzoate (Ar = 4-($COOCH_2CH_3$)phenyl)

The synthesis of the title compound started with reaction of 4-cyanobenzonitrile oxide with commercial 4-vinylbenzoic acid, and the ethyl ester was formed during the formation of the imidazoline;
colorless crystalline solid; m.p. 213-215 °C

Example 235: 4-(3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazol-5-yl)benzoic Acid (Ar = 4-(COOH)phenyl)

The title compound was prepared by hydrolysis of the ester of the previous example with aqueous sodium hydroxide;
colorless crystalline solid; m.p. 263-265 °C

Example 236: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(2-naphthyl)-4,5-dihydro-isoxazole (Ar = 2-naphthyl)

Colorless crystalline solid; m.p. 244-246 °C

Example 237: 5-(3-Chlorophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazole (Ar = 3-chlorophenyl)

Colorless crystals; m.p. 190-191 °C

Example 238: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(3-fluorophenyl)-4,5-dihydro-isoxazole (Ar = 3-fluorophenyl)

Colorless crystals; m.p. 193-194 °C

Example 239: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-fluorophenyl)-4,5-dihydro-isoxazole (Ar = 4-fluorophenyl)

Colorless crystals; m.p. 218 °C

Example 240: 5-(2,6-Difluorophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazole (Ar = 2,6-difluorophenyl)

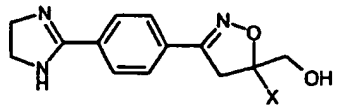
Colorless crystals; m.p. 195-196 °C

Example 241: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-methylphenyl)-4,5-dihydro-isoxazole (Ar = 4-methylphenyl)

Colorless crystalline solid; m.p. 220-221 °C

Example 242: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(3-methylphenyl)-4,5-dihydro-isoxazole (Ar = 3-methylphenyl)

Colorless crystalline solid; m.p. 178-179 °C



Examples 243 - 244

Example 243: (3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-4,5-dihydro-isoxazol-5-yl)methanol (X = H)

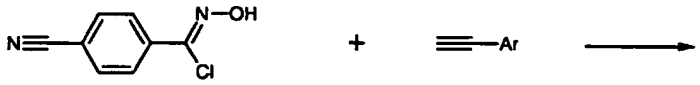
The title imidazoline was prepared in the same manner as described before starting from 2-propen-1-ol;

colorless crystalline solid; m.p. 211-213 °C

Example 244: (3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-hydroxymethyl-4,5-dihydro-isoxazol-5-yl)methanol Hydrochloride (X = CH_2OH)

The title compound was prepared in the same manner as described above starting from commercial 2-methylen-propan-1,3-diol;

colorless crystalline solid; m.p. 202-203 °C



Intermediate 13

Examples 245 - 258

The following Examples 245-258 were prepared substantially in the same manner as

described for the previous examples starting from arylacetylene derivatives which were either commercially available or prepared by known procedures.

Example 245: **3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-phenyl-isoxazole (Ar = phenyl)**

Colorless amorphous solid; m.p. 218-219 °C

Example 246: **3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(3-(phenylmethoxy)phenyl)-isoxazole (Ar = 3-benzyloxyphenyl)**

The intermediate nitrile was prepared by reaction of 4-cyanobenzonitrile oxide with commercial 3-ethynylphenol followed by alkylation of the resulting isoxazole with benzyl bromide;

colorless crystals; m.p. 200-201 °C

Example 247: **3-(3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-isoxazol-5-yl)phenol (Ar = 3-hydroxyphenyl)**

The title compound was obtained as an additional product during the formation of the imidazoline of Example 246 by cleavage of the benzylether under the acidic reaction conditions;

colorless crystals; m.p. 279-281 °C

Example 248: **3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(3-propoxyphenyl)-isoxazole (Ar = 3-propoxyphenyl)**

The intermediate nitrile was prepared in the same manner as described for Example 246 including alkylation with propyl iodide;

colorless crystals; m.p. 260-265 °C

Example 249: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(3-methoxyphenyl)-isoxazole (Ar = 3-methoxyphenyl)

The intermediate nitrile was prepared in the same manner as described for the previous example including alkylation with methyl iodide;

pale yellow amorphous solid; m.p. 150-152 °C

Example 250: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-fluorophenyl)-isoxazole Hydrochloride (Ar = 4-fluorophenyl)

Colorless crystals; m.p. 311-313 °C

Example 251: 5-(4-Chlorophenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-isoxazole (Ar = 4-chlorophenyl)

Colorless crystals; m.p. 248-250 °C

Example 252: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-methylphenyl)-isoxazole (Ar = 4-methylphenyl)

Colorless amorphous solid; m.p. 221-223 °C

Example 253: 2-(3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-isoxazol-5-yl)pyridine (Ar = 2-pyridinyl)

Beige crystalline solid; m.p. 260-262 °C

Example 254: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-propoxyphenyl)-isoxazole Hydrochloride (Ar = 4-propoxyphenyl)

Colorless crystals; m.p. 270-273 °C

Example 255: 5-(4-Butylphenyl)-3-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-isoxazole Hydrochloride (Ar = 4-butylphenyl)

Colorless crystals; m.p. 287-289 °C

Example 256: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(2-ethylphenyl)-isoxazole (Ar = 2-ethylphenyl)

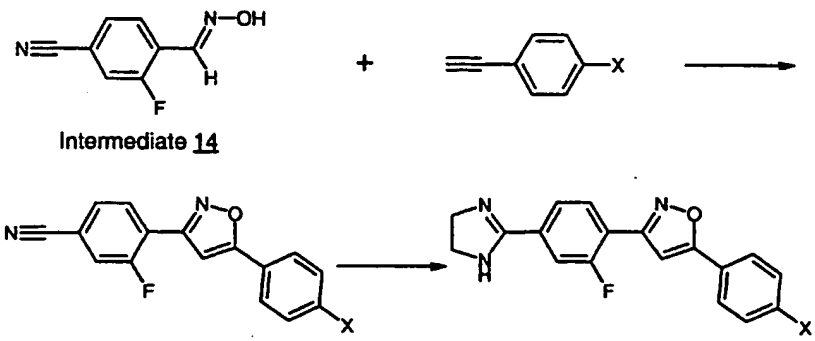
The title compound was prepared from 1-ethyl-2-ethynylbenzene which was obtained by Pd catalyzed coupling of 1-ethyl-2-iodobenzene with (trimethylsilyl)ethyne followed by cleavage of the trimethylsilyl group with tetrabutylammonium fluoride; colorless crystals; m.p. 143-144 °C

Example 257: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(2-trifluoromethylphenyl)-isoxazole (Ar = 2-trifluoromethylphenyl)

The intermediate 1-ethynyl-2-trifluoromethylbenzene (Bull. Chem. Soc. Jpn. 61 (1988), 1625) was prepared from 1-iodo-2-trifluoromethylbenzene in the same manner as described for the previous example and used to prepare the title imidazoline; colorless crystals; m.p. 172-174 °C

Example 258: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-5-(4-methoxyphenyl)-isoxazole Hydrochloride (Ar = 4-methoxyphenyl)

Colorless crystalline solid; m.p. 275-277 °C



Intermediate 14

Examples 259 - 260

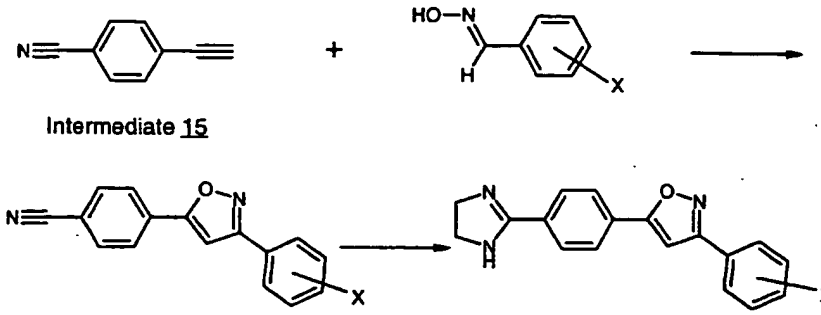
The imidazolines of Examples 259 and 260 were prepared from 2-fluoro-4-cyanobenzaldoxime (Intermediate 14; J. Med. Chem. 40 (1997), 2064) in the same manner as described for the previous examples. 4-Cyano-2-fluorobenzonitrile oxide was generated from the oxime by oxidation with commercial aqueous sodium hypochlorite solution giving the intermediate 3-(4-cyano-2-fluorophenyl)isoxazoles.

Example 259: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)-2-fluorophenyl)-5-phenyl-isoxazole (X = H)

Colorless crystals; m.p. 196-198 °C

Example 260: 3-(4-(4,5-Dihydro-1H-imidazol-2-yl)-2-fluorophenyl)-5-(4-fluorophenyl)-isoxazole (X = F)

Colorless crystals; m.p. 243-245 °C



Intermediate 15

Examples 261 - 266

The compounds of the Examples 261-266 were prepared in a similar manner starting from the acetylene of Intermediate 15 (Synthesis 1980, 627), which reacted with benzonitrile oxides generated from the corresponding benzaldoximes either by oxidation with aqueous sodium hypochlorite solution or by chlorination with N-chlorosuccinimide followed by dehydrochlorination with triethylamine according to a procedure known from the literature (J. Org. Chem. 45 (1980), 3916). The benzaldoximes were either commercially available or prepared from benzaldehydes and hydroxylamine by standard procedures. The imidazoline ring was formed as described above for the previous isoxazoles.

Example 261: 5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-phenyl-isoxazole (X = H)

Colorless crystals; m.p. 228-230 °C

Example 262: 3-(2-Bromophenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-isoxazole (X = 2-Br)

Colorless crystals; m.p. 152-154 °C

Example 263: 3-(2,6-Dichlorophenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-isoxazole (X = 2,6-Cl_2)

Colorless crystals; m.p. 219-220 °C

Example 264: 3-([1,1'-Biphenyl]-4-yl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-isoxazole Hydrochloride (X = 4-phenyl)

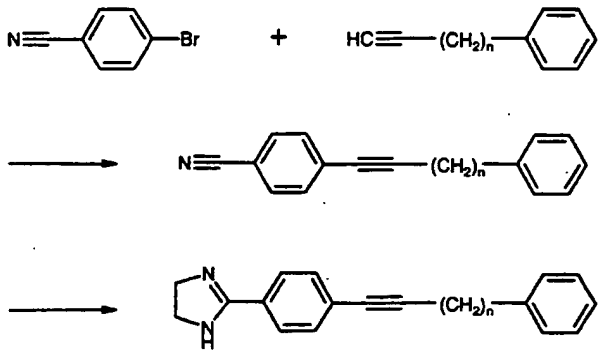
Colorless crystalline solid; m.p. > 300 °C

Example 265: 3-(3,4-Dichlorophenyl)-5-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-isoxazole Hydrochloride (X = 3,4-Cl_2)

Colorless crystals; m.p. > 300 °C

Example 266: 5-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-3-(4-fluorophenyl)-isoxazole Hydrochloride (X = 4-F)

Colorless crystals; m.p. 325-327 °C



Examples 267 - 269

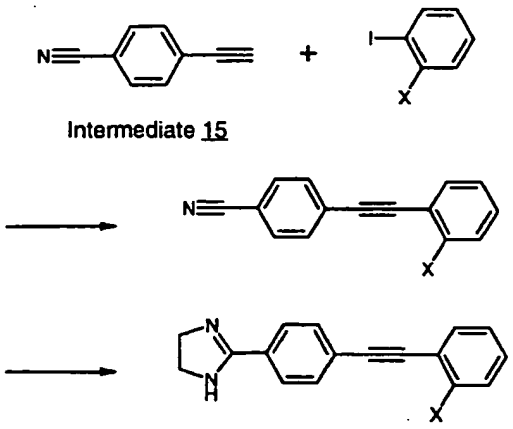
The compounds of Examples 267-269 were prepared by coupling of 4-bromobenzonitrile with the corresponding terminal acetylenes which was achieved by heating in triethylamine in the presence of $Pd(PPh_3)_4$ and Cu(I) bromide. The imidazolines were prepared by saturating an ethanolic solution of the intermediate nitriles with hydrogen chloride followed by treatment with 1,2-diaminoethane.

Example 267: 2-(4-(Phenylethynyl)phenyl)-4,5-dihydro-1H-imidazole (n = 0)
Brown resin

Example 268: 2-(4-(4-Phenylbut-1-yn-1-yl)phenyl)-4,5-dihydro-1H-imidazole Hydrochloride (n = 2)
Beige crystalline solid; m.p. 188-190 °C

Example 269: 2-(4-(5-Phenylpent-1-yn-1-yl)phenyl)-4,5-dihydro-1H-imidazole Hydrochloride (n = 3)

Colorless crystals; m.p. 188-190 °C



Intermediate 15

Examples 270 - 271

4-Ethynylbenzonitrile (Intermediate 15; prepared according to Synthesis 1980, 627) was coupled with iodobenzenes by heating in triethylamine in the presence of $PdCl_2(PPh_3)_2$ and Cu(I) iodide, and the imidazolines of Example 270 and 271 were obtained from the resulting intermediate nitriles as described for the previous examples.

Example 270: 2-[4-((2-Methylphenyl)ethynyl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride (X = CH_3)

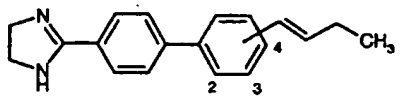
prepared from 1-ethynyl-2-methylbenzene (J. Org. Chem. 43 (1978), 358); colorless crystalline solid; m.p. 324-326 °C

Example 271: 2-[4-((2-Ethylphenyl)ethynyl)phenyl]-4,5-dihydro-1H-imidazole

Hydrochloride (X = CH_2CH_3)

prepared from 1-ethyl-2-ethynylbenzene;

colorless crystals; m.p. 314-316 °C



Examples 272 - 274

The imidazolines of Examples 272-274 were prepared by Suzuki coupling reaction as described for the Examples 126-144 with the corresponding (formylbenzene)boronic acids followed by Wittig reaction methodology using triphenylpropylphosphonium bromide. The reaction sequence included protection of the imidazoline nitrogen by a benzyloxycarbonyl group.

Example 272: **2-(2'-(1-Buten-1-yl)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole**

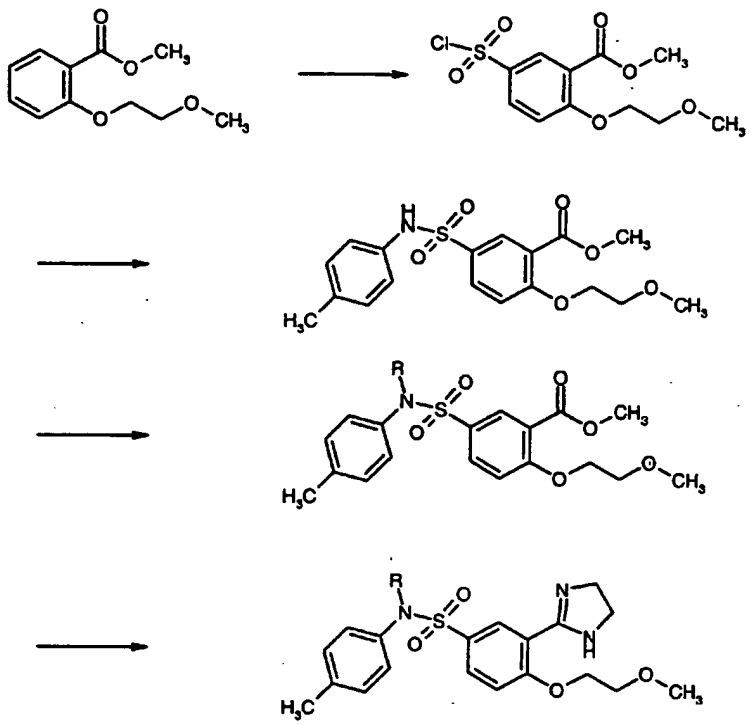
Brown resin

Example 273: **2-(3'-(1-Buten-1-yl)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole**

Brown resin

Example 274: **2-(4'-(1-Buten-1-yl)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole**

Brown resin



Examples 275 - 276

The compounds of the Examples 275 and 276 were prepared starting from methyl 2-(2-methoxyethoxy)benzoate (WO 98/49166). The ester was sulfonated with chlorosulfuric acid and the resulting sulfonyl chloride treated with p-toluidine to give the intermediate sulfonamide. The related N-methylsulfonamide (R = CH_3) was obtained by alkylation with methyl iodide, and the title imidazolines were prepared with 1,2-diaminoethane followed by cyclization with diethylaminomethylpolystyrene and trimethylsilyl iodide.

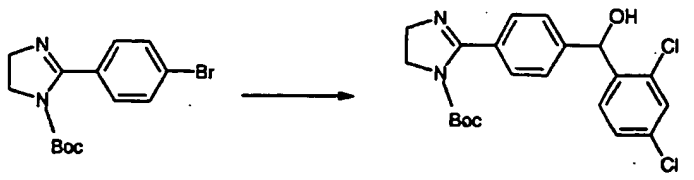
Example 275: **3-(4,5-Dihydro-1H-imidazol-2-yl)-4-(2-methoxyethoxy)-N-(4-methylphenyl)benzenesulfonamide (R = H)**

Colorless crystals; m.p. 194-196 °C

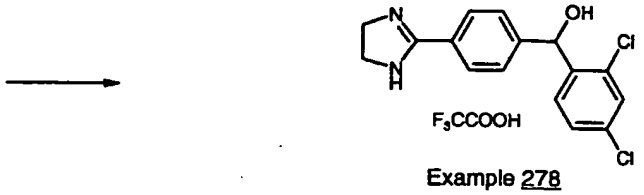
Example 276: **3-(4,5-Dihydro-1H-imidazol-2-yl)-4-(2-methoxyethoxy)-N-methyl-N-(4-methylphenyl)benzenesulfonamide (R = CH_3)**

Beige amorphous solid

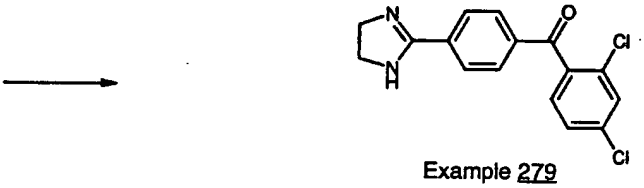
The N-protected imidazoline of Intermediate 16 was prepared from the compound of Intermediate 8 and treated with butyl lithium. The compound of Example 277 was obtained by reaction of the aryllithium intermediate with 2,4-dichlorobenzaldehyde. After deprotection with trifluoroacetic acid the ketone of Example 279 was prepared by oxidation with Mn(IV) oxide.



Intermediate 16 Example 277



Example 278



Example 279

Example 277: tert. Butyl 2-(4-((2,4-Dichlorophenyl)hydroxymethyl)phenyl)-4,5-dihydro-1H-imidazole-1-carboxylate

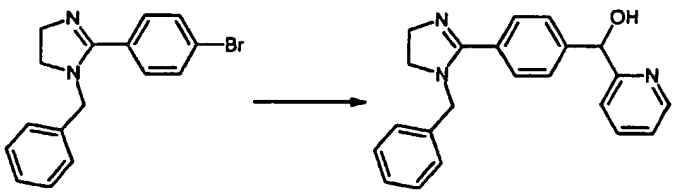
Pale yellow crystalline solid; m.p. 151-153 °C

Example 278: (2,4-Dichlorophenyl)-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)methanol Trifluoroacetate

Colorless crystalline solid; m.p. 187-188 °C

Example 279: (2,4-Dichlorophenyl)-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)methanone

Colorless crystalline solid



Intermediate 17 Example 280

Example 280: (4-(1-Phenylmethyl-4,5-dihydro-1H-imidazol-2-yl)phenyl)-(pyridin-2-yl)methanol

The imidazoline of Intermediate 17 was prepared from 4-bromobenzonitrile and N-benzyl-1,2-diaminoethane and treated with butyl lithium followed by 2-pyridinecarboxaldehyde;

beige amorphous solid

Intermediate 18 Examples 281 - 282

The imidazoline of Intermediate 18 (J. Heterocyclic Chem. 27 (1990), 803) was used to prepare the pyrrole derivatives of the Examples 281 and 282 by heating in acetic acid with commercial 2,5-diethoxytetrahydrofuran or 2,5-dimethoxy-3-

formyltetrahydrofuran, respectively.

Example 281: 2-(4-(1H-Pyrrol-1-yl)phenyl)-4,5-dihydro-1H-imidazole (X = H)

Beige crystalline solid

Example 282: 1-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1H-pyrrole-3-carbaldehyde (X = CHO)

Pale yellow crystalline solid

Intermediate 18 Examples 283 - 284

The Examples 283 and 284 were prepared from the imidazoline of Intermediate 18 by reaction with benzoyl chloride or phenylisocyanate, respectively.

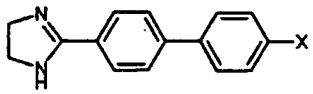
Example 283: N-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)benzamide Trifluoroacetate (X = NHCO)

Pale yellow crystalline solid; m.p. 243 °C

Example 284: N-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl-N'-phenyl-urea Trifluoroacetate (X = NHCONH)

Colorless crystalline solid; m.p. 164-166 °C

The following examples were prepared from benzonitrile or benzoic acid derivatives which are either commercially available or are known compounds and were synthesized by known procedures from the literature. The formation of the imidazoline was carried out by one of the methods described before.



Examples 285 - 293

Example 285: 2-(4'-Pentyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (X = $(CH_2)_4CH_3$)

prepared from commercial (4'-pentyl-[1,1'-biphenyl]-4-yl)carbonitrile

colorless crystals; m.p. 212-214 °C

Example 286: 2-(4'-Methoxy-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole (X = OCH_3)

prepared from (4'-methoxy-[1,1'-biphenyl]-4-yl)carbonitrile (J. Org. Chem. 53 (1988), 1496);

colorless crystals

Example 287: 2-(4'-Methyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (X = CH_3)

prepared from (4'-methyl-[1,1'-biphenyl]-4-yl)carbonitrile (Tetrahedron 50 (1994), 8301);

colorless amorphous solid

Example 288: (4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)carbonitrile (X = CN)

prepared from commercial [1,1'-biphenyl]-4,4'-dicarbonitrile;
colorless amorphous solid

Example 289: 4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-ol Hydrochloride (X = OH)

prepared from commercial (4'-hydroxy-[1,1'-biphenyl]-4-yl)carbonitrile;
colorless crystalline solid; m.p. > 270 °C

Example 290: 2-(4'-(2-Methoxyethoxy)-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole (X = $OCH_2CH_2OCH_3$)

The nitrile intermediate (EP 47453) was prepared by alkylation of commercial (4'-hydroxy-[1,1'-biphenyl]-4-yl)carbonitrile with 2-methoxyethyl bromide;
beige crystalline solid

Example 291: 2-(4'-Heptyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole (X = $(CH_2)_6CH_3$)

prepared from commercial (4'-heptyl-[1,1'-biphenyl]-4-yl)carbonitrile;
colorless crystalline solid; m.p. 177-178 °C

Example 292: 2-(4'-Nitro-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (X = NO_2)

prepared from (4'-nitro-[1,1'-biphenyl]-4-yl)carboxylic acid (Bioorg. Med. Chem.

Lett. 8 (1998), 2395);

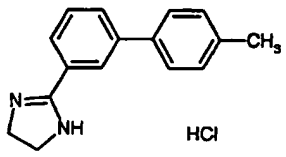
beige crystalline solid

Example 293: 2-(4'-Ethyl-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-imidazole Hydrochloride (X = CH_2CH_3)

prepared from commercial (4'-ethyl-[1,1'-biphenyl]-4-yl)carboxylic acid;

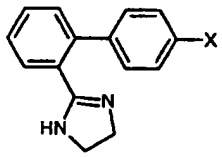
colorless crystalline solid; m.p. 210-211 °C

Example 294: 2-(4'-Methyl-[1,1'-biphenyl]-3-yl)-4,5-dihydro-1H-imidazole Hydrochloride



prepared from (4'-methyl-[1,1'-biphenyl]-3-yl)carbonitrile (J. Med. Chem. 34 (1991), 2525);

colorless crystalline solid; m.p. 178-180 °C



Examples 295 - 297

Example 295: 2-(4'-Methyl-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole

Hydrochloride (X = CH_3)

prepared from (4'-methyl-[1,1'-biphenyl]-2-yl)carbonitrile (J. Med. Chem. 34 (1991), 2525);

colorless crystals; m.p. 193 °C

Example 296: (2'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)methanol Hydrochloride (X = CH_2OH)

prepared from (4'-hydroxymethyl-[1,1'-biphenyl]-2-yl)carbonitrile (WO 94/03449);

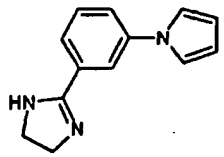
beige crystalline solid; m.p. 210-235 °C (dec.)

Example 297: 2-(4'-((2-Methoxyethoxy)methoxy)-[1,1'-biphenyl]-2-yl)-4,5-dihydro-1H-imidazole Hydrochloride (X = $CH_2OCH_2CH_2OCH_3$)

The intermediate nitrile was prepared by alkylation of (4'-hydroxymethyl-[1,1'-biphenyl]-2-yl)carbonitrile with 2-methoxyethyl bromide;

pale yellow crystalline solid

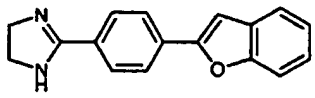
Example 298: 2-(3-(1H-Pyrrol-1-yl)phenyl)-4,5-dihydro-1H-imidazole



prepared from commercial 3-(1H-pyrrol-1-yl)benzonitrile;

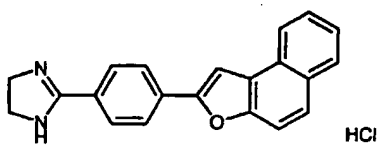
pale yellow crystalline solid; m.p. 160-161 °C

Example 299: 2-[4-(Benzofuran-2-yl)phenyl]-4,5-dihydro-1H-imidazole

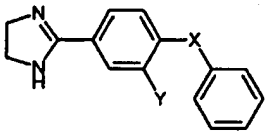


prepared from 4-(benzofuran-2-yl)benzonitrile (Liebigs Ann. Chem. 1974, 523);
colorless crystals; m.p. 238 °C

Example 300: 2-[4-(Naphtho[2,1-b]furan-2-yl)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride



prepared from 4-(naphtho[2,1-b]furan-2-yl)benzonitrile (Liebigs Ann. Chem. 1974, 523);
yellow crystalline solid; m.p. > 300 °C



Examples 301 - 304

Example 301: 2-(4-(Phenylsulfonyl)phenyl)-4,5-dihydro-1H-imidazole (X = SO_2, Y = H)

prepared from 4-(phenylsulfonyl)benzonitrile (J. Org. Chem. 54 (1989), 4691);
colorless crystals; m.p. 170-173 °C

Example 302: 2-[4-(N-Methyl-N-phenylamino)phenyl]-4,5-dihydro-1H-imidazole (X = NCH_3, Y = H)

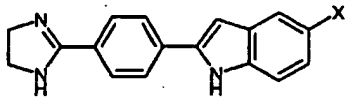
prepared from (4-cyanophenyl)-methyl-phenylamine (J. Org. Chem. 62 (1997), 1568);
colorless crystals; m.p. 178-180 °C

Example 303: 4-(4,5-Dihydro-1H-imidazol-2-yl)-N-phenyl-benzamide Hydrochloride (X = CONH, Y = H)

prepared from 4-cyano-N-phenylbenzamide (Tetrahedron 37 (1981), 4171);
beige crystalline solid; m.p. 300-303 °C

Example 304: 4-(4,5-Dihydro-1H-imidazol-2-yl)-2-fluoro-N-phenyl-benzamide (X = CONH, Y = F)

The intermediate 4-cyano-2-fluoro-N-phenylbenzamide was prepared by condensation of 4-cyano-2-fluorobenzoic acid (WO 96/01255) with aniline;
colorless crystalline solid; m.p. 208-210 °C



Examples 305 - 306

Example 305: 2-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1H-indole (X = H)

prepared from 4-(1H-indol-2-yl)benzonitrile (J. Org. Chem. 59 (1994), 4250);

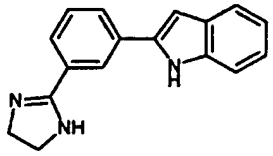
yellow crystalline solid; m.p. 264-265 °C

Example 306: 5-Chloro-2-(4-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-1H-indole (X = 5-Cl)

The intermediate 5-chloro-4-(1H-indol-2-yl)benzonitrile was prepared from (4-chlorophenyl)hydrazine and 4-cyanoacetophenone.

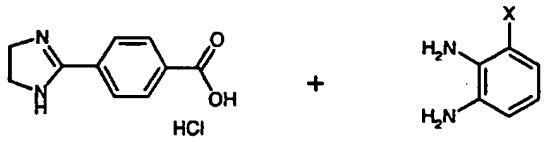
Yellow crystalline solid; m.p. 285 °C

Example 307: 2-(3-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1H-indole

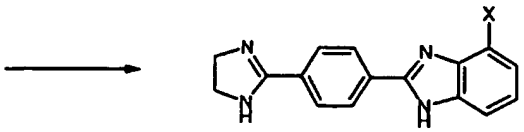


The intermediate 3-(1H-indol-2-yl)benzonitrile was prepared from phenylhydrazine and 3-cyanoacetophenone.

Yellow crystalline solid; m.p. 249-251 °C



Intermediate 19



Examples 308 - 309

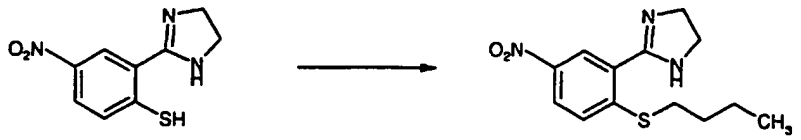
The imidazolines of the Examples 308 and 309 were prepared from the compound of Intermediate 19 (WO 98/31661) and the corresponding 1,2-diaminobenzenes by heating in hydrochloric acid.

Example 308: 2-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-1H-benzimidazole (X = H)

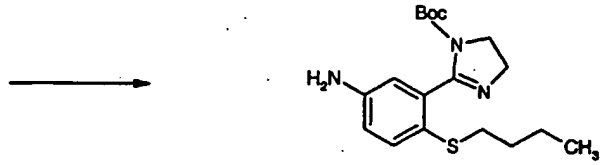
Brown crystalline solid

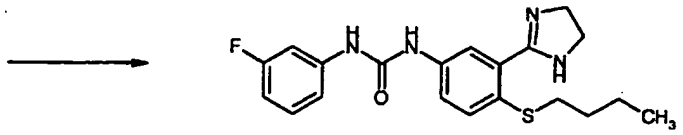
Example 309: 2-(4-(4,5-Dihydro-1H-imidazol-2-yl)phenyl)-4-hydroxy-1H-benzimidazole Hydrochloride (X = OH)

Brown crystalline solid; m.p. 168-170 °C (dec.)



Intermediate 20 Intermediate 21





Example 310

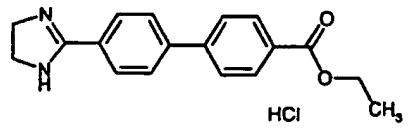
Intermediate 21: 2-(2-Butylthio-5-nitrophenyl)-4,5-dihydro-1H-imidazole

The imidazoline of Intermediate 20 is known from the literature (Liebigs Ann. Chem. 1975, 1994) and was alkylated with butyl bromide;
brown crystalline solid; m.p. 265 °C

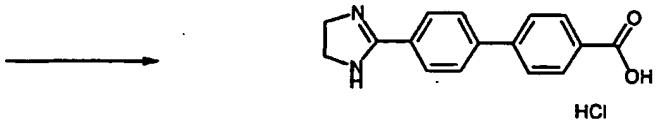
Example 310: N-(4-Butylthio-3-(4,5-dihydro-1H-imidazol-2-yl)phenyl)-N'-(3-fluorophenyl)-urea

After N-protection of the imidazoline of Intermediate 21 by tert.-butoxycarbonyl the nitro group was reduced with $Na_2S_2O_4$, and the title compound was obtained by reaction with (3-fluorophenyl)isocyanate.

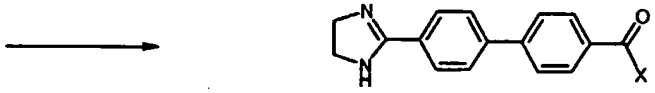
Colorless crystalline solid; m.p. 145 °C



Example 311



Example 312



Examples 313 - 317

Example 311: Ethyl (4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)carboxylate Hydrochloride

The title compound was prepared from ethyl (4'-cyano-[1,1'-biphenyl]-4-yl)carboxylate (J. Org. Chem. 56 (1991), 1445);

colorless crystalline solid

Example 312: (4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)carboxylic Acid Hydrochloride

prepared by hydrolysis of the ester from the previous example;

colorless crystalline solid

The following examples were prepared from the carboxylic acid of Example 312 by condensation with methanol or the corresponding amines. The reaction was carried out with oxalyl chloride / DMF.

Example 313: Methyl (4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)carboxylate Hydrochloride (R = OCH_3)
prepared with methanol;
beige amorphous solid

Example 314: N-Phenyl-(4'-(4,5-dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)-carboxamide Hydrochloride (R = $NH(C_5H_6)$)
prepared by condensation with aniline;
beige crystalline solid; m.p. 292-295 °C

Example 315: Ethyl [((4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)carbonyl)amino]acetate Hydrochloride (R = $NHCH_2COOCH_2CH_3$)
prepared by condensation with glycine ethylester hydrochloride;
beige crystalline solid; m.p. 230-233 °C

Example 316: Methyl (S)-2-[((4'-(4,5-Dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)carbonyl)amino]-3-phenylpropionate Hydrochloride (R = (S)-$NHCH(COOCH_3)CH_2(C_6H_5)$)
prepared with (S)-phenylalanine methylester hydrochloride;
beige amorphous solid

Example 317: N-Hexyl-(4'-(4,5-dihydro-1H-imidazol-2-yl)-[1,1'-biphenyl]-4-yl)-carboxamide Hydrochloride (R = $NH(CH_2)_5CH_3$)

prepared by condensation with hexylamine;
beige crystalline solid; m.p. 168-170 °C

The pharmacological activity of compounds of the present invention may be determined by methods well known in the art and by the assays disclosed herein.

ASSAYS

BTC6, F7 Insulinoma Cell Screening Models

BTC6,F7 are cultured in DMEM 4.5g/l glucose with the following supplements: 15%(v/v) equine serum; 2.5% (v/v) FCS; and 50 U/ml Penicillin/ 50 µg/ml Streptomycin.

A) Adherent BTC6,F7 cells

BTC6,F7 are seeded after trypsinization to 30.000 cells/well in a 96 well multiplate. The cells grow to 50 % confluence and at day 2 or 3 after seeding, the insulin secretion experiments were performed as follows:

Discard the supernatant of the 96 well plates after the cells have been seeded, wash 3 times with EBSS (Earl's balanced salt solution) (0 mM glucose)/ 0.1 % BSA and incubate in the EBSS solution 30 min at 5% CO_2, 37°C.

The experiments with the compounds were run in the presence of 10 mM glucose and also in the absence of glucose in different concentrations. Incubation time is 1 hour. The supernatante is filtered and the insulin amounts measured by radioimmunoassay using an antibody directed against rat insulin.

B) Dissociated BTC6,F7 cells

BTC6,F7 cells at 50 % confluence were dislodged using enzyme free cell dissociation solution. Dislodged cells were dissociated by pressing the cell suspension through a needle (25 gauge). Cells were washed three times in EBSS (0 mM glucose)/0.1% BSA and insulin secretion experiments are performed as described above.

Dose response titrations on the agonists described revealed EC_{50} values of < 10 mM, preferably < 1mmol.

Rat Islet Assay

The number of islets of three rats is usually sufficient to test 8 compounds including standards.

Solutions

1. 100 ml EBSS (Earl's balanced salt solution): For example, as commercially available Cat. No. BSS-008-B (Specialty Media) without Glucose & Phenol Red, with 0.1% BSA, other comparable commercially available media are acceptable.

2. 100 ml EBSS/BSA buffer + 130.8 mg D(+)-Glucose monohydrate (MW: 198.17)

(=3.3 mM final concentration).

3. 100 ml EBSS/BSA buffer + 661.8 mg D(+)-Glucose monohydrate (MW: 198.17)

(=16.7 mM final concentration).

4. 100 ml EBSS (Earl's balanced salt solution). For example, as commercially available,Cat. No. BSS-008-B (Specialty Media) without Glucose & Phenol Red, with 0.1% BSA, with 0.6 % DMSO; other comparable solutions may be used as well;

Dilution of compounds:

Each dilution of compound has to be double concentrated as it will be diluted 1 + 1 by EBSS/BSA + Glucose (either high Glucose, 16.7 mM final conc. or low Glucose, 3.3 mM final conc.) in a 24 -well tissue culture plate (or other appropriate tissue culture receptacle, if desired).

A stock solution of the compound to be tested of 10 mM in DMSO is made, and the following solutions made for the compounds to be tested, and for standards.

Tube No.	Concentration (μM)	final Concentration (μM)	Dilution (μl)
1	200	100	40 μl of stock + 2000 μl EBSS/BSA
2	60	30	900 μl of tube 1 + 2100 μl EBSS/BSA
3	20	10	300 μl of tube 1 + 2700 μl EBSS/BSA/ 0.6 % DMSO
4	6	3	300 μl of tube 2 + 2700 μl EBSS/BSA/ 0.6 % DMSO
5	2	1	300 μl of tube 3 + 2700 μl EBSS/BSA/ 0.6 % DMSO
6	0.6	0.3	300 μl of tube 4 + 2700 μl EBSS/BSA/ 0.6 % DMSO
7	0.2	0.1	300 μl of tube 5 + 2700 μl EBSS/BSA/ 0.6 % DMSO
8	0.06	0.03	300 μl of tube 6 + 2700 μl EBSS/BSA/

			0.6 % DMSO

Culture dishes are prepared (untreated, 100 x 20 mm, one per two compounds) with 10 ml EBSS/BSA and 10 ml low glucose EBSS/BSA or similar preparative solution and place in an incubator at 37°C, 5 % CO_2, for at least 15 min.

Preparation of Rat islets in culture dishes:

Approximately half of an islet is selected with a 100 µl pipette and transfered to a prepared culture dishe with EBSS/BSA/low Glucose by using binoculars (magnification about 30 x.

The dish is put back into the incubator (37°C, 5 % CO_2) for preincubation (30 min)

If a 24 well plate is used for the assay, the dilutions are distributed (500 µl each) as shown in the scheme below.

500 µl of EBSS/BSA + 0.6 % DMSO (0 = Control).

0 1	**0** 2	**0.03** 3	**0.03** 4	**0.1** 5	**0.1** 6
0.3 7	**0.3** 8	**1** 9	**1** 10	**3** 11	**3** 12
10 13	**10** 14	**30** 15	**30** 16	**0** 17	**0** 18

0.1	0.1	1	1	10	10
19	20	21	22	23	24

EBSS/BSA/ high Glucose, 500 µl is added to wells 1-16, and EBSS/BSA/ low Glucose, 500 µl is added to wells 17-24.

This scheme is repeated with the other compounds in tissue culture plates and the plates are placed into the incubator (37°C, 5 % CO_2) for at least 15 min.

The culture dish with the second half of the islets is taken out of the incubator. The rest of the islet is picked up with a 100 µl pipette and placed into the second of the prepared culture dishes with EBSS/BSA/low Glucose using binoculars, and placed back into the incubator (37°C, 5 % CO_2) for preincubation (30 min).

Take out the tissue culture plates 1 and 2 and the first preincubated islets. Place 8 islets into each well by using a 10 µl pipette and binoculars (general guideline-magnification about 40 x), generally trying to select islets of similar size which are not digested. The plates are placed back in the incubator (37°C, 5 % CO_2) for 90 min.

Remove the second of the overnight cultured culture dishes with islets from incubator. Approximately half of the islets are placed into the 3rd of the prepared culture dishes with EBSS/BSA/low Glucose with a 100 µl pipette and using binoculars (general guideline-magnification about 30 x), then placed back into the incubator (37°C, 5 % CO_2) for preincubation (30 min).

The 24 -well tissue culture plates 3 and 4 and the second preincubated islets culture dish are removed from the incubator and 8 islets placed into each well by using a 10 µl pipette and binoculars (magnification about 40 x), again selecting islets of similar size which are not digested. Put the plates back to the incubator (37°C, 5 % CO_2) for 90 min.

Take the culture dish with the second half of the islets out of the incubator. with a 100 µl pipette into the 4th of the prepared culture dishes with EBSS/BSA/low Glucose by using binoculars (magnification about 30 x) and put them back into the incubator (37°C, 5 % CO_2) for preincubation (30 min)

Take out the 24 -well tissue culture plates 5 and 6 and the 3rd preincubated islets culture dish. Place 8 islets into each well with a 10 µl pipette by using binoculars (magnification about 40 x). Put the plates back into the incubator (37°C, 5 % CO_2) for 90 min.

Take out the 24 -well tissue culture plates 7 and 8 and the last preincubated islets culture dish. Place 8 islets into each well with a 10 µl pipette by using binoculars (magnification about 40 x). Put the plates back to the incubator (37°C, 5 % CO_2) for 90 min.

When 90 minutes of incubation are over, transfer approximately 300 µl of each well into one well of the 96 well filter plate and by using a vacuum pump filter it into a 96 well Microplate. 4 of the 24 -well tissue culture plates cover one filterplate and

96-well-Microplate.

The insulin secreted by the islets is measured in a RIA after dilution (1:5).

Intravenous Glucose Tolerance Test

This test is used to examine in vivo efficacy of compounds of the present invention on insulin secretion and blood glucose at hyperglycemia.

The intravenous glucose tolerance test (IVGTT) is performed in overnight fasted anesthetized male wistar rats weighing 280-350g. Under pentobarbitone anesthesia (50 mg/kg ip) polyethylene catheters are placed in the left jugular vein and in the left common carotid artery. Glucose (10% solution) is administered intravenously at a dose of 0.5 g/kg, followed directly by an iv injection of the compound to be tested.

Blood samples are drawn before and 3, 6, 10, 15, 30 and 45 min after glucose administration, centrifuged and the obtained serum is stored at -20°C for analytics. Test compounds are examined along with a reference (positive control) and a vehicle control with n=8 animals per group. Glucose is determined by the hexokinase method, and insulin via radioimmunoassay (RIA) from serum.

In order to examine the effects of test compounds on insulin and blood glucose at euglycemia in vivo, the protocol of the IVGTT as described above is used except for the administration of intravenous glucose.

The compounds of Formula I are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of Formula I and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 500 mg, more usually about .5 to about 200 mg, of the active ingredient. However, it will be understood that the therapeutic dosage administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. The

compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, topical, intravenous, intramuscular or intranasal routes. For all indications, a typical daily dose will contain from about 0.05 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.1 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg. However, for topical administration a typical dosage is about 1 to about 500 mg compound per cm^2 of an affected tissue. Preferably, the applied amount of compound will range from about 30 to about 300 mg/cm^2, more preferably, from about 50 to about 200 mg/cm^2, and, most preferably, from about 60 to about 100 mg/cm^2.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	25
starch, dried	425
magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 10 mg of active ingredient are made up as follows:

Active ingredient	10 mg
Starch	160 mg

Microcrystalline cellulose	100 mg
Polyvinylpyrrolidone (as 10% solution in water)	13 mg
Sodium carboxymethyl starch	14 mg
Magnesium stearate	3 mg
Total	300 mg

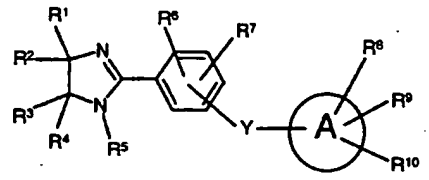
The active ingredient, starch and cellulose are mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders and passed through a sieve. The granules so produced are dried and re-passed through a sieve. The sodium carboxymethyl starch and magnesium stearate are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 300 mg.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since they are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention.

Claims

We claim

1. A compound of Formula (I):



I

wherein

R^1, R^2, R^3, and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^3 and R^4, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

R^5 is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

R^6 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy,

hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy;

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted phenyloxy, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_m$, $CH_3(CH_2)_p$-Z^1-$(CH_2)_q$-Z^2-, and Z^3-$(CH_2)_{q'}$-Z^2- ;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  , SO_2, sulphoximino, or NR^{11};

Z^3 is hydroxy, protected hydroxy, $NR^{12}R^{13}$, protected amino, SH, or protected SH;

Y is selected from the group consisting of -NR'CONR''- or $-(CH_2)_kW(CH_2)_b$-, wherein $-(CH_2)_kW(CH_2)_b$-, is optionally substituted with C_{1-4} alkyl or hydroxy;

k is independently 0, 1, 2, 3, or 4;

b is independently 0, 1, 2, 3, or 4;

provided that the sum of k and b together is not more than 4;

W is selected from the group consisting of a bond, O, S, SO_2, SO, SO_2NR''', $NR'''SO_2$, NR'''', $CONR'''$, $NR'''CO$, -C=C-, -C≡C-, and C=O,

R', R'' and R''' are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and benzyl;

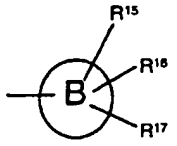
R'''' is selected from the group consisting of hydrogen, C_{1-8} alkyl, benzyl, and an amino protecting group;

the group A is a monocyclic or bicyclic ring selected from

benzene, naphthalene, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, quinoline, isoquinoline, 1,5-naphthyridine, 1,6-naphthyridine, 1,7-naphthyridine, 1,8-naphthyridine, 2,6-naphthyridine, 2,7-naphthyridine, quinazoline, quinoxaline, phthalazine, cinnoline, furan, thiophene, benzofuran, benzo[b]thiophene, pyrrole, indole, imidazole, benzimidazole, imidazo[4,5-b]pyridine, imidazo[4,5-c]pyridine, oxazole, benzoxazole, oxazolo[5,4-b]pyridine, oxazolo[4,5-b]pyridine, oxazolo[5,4-c]pyridine, oxazolo[4,5-c]pyridine, isoxazole, 4,5-dihydroisoxazole, benzo[d]isoxazole, thiazole, benzothiazole, pyrazole, indazole, isothiazole, benzo[d]isothiazole, 1,2,3-triazole, benzotriazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, benzo[1,2,5]oxadiazole, 1,3,4-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,2,3-thiadiazole, benzo[1,2,5]thiadiazole, 1H-tetrazole, imidazo[1,2-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-b]pyridazine, imidazo[1,2-a]pyrimidine, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole, imidazo[1,2-a]imidazole,

which may be fused with a benzene ring to form a tricyclic ring;

R^8 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkynyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, cyano, nitro, formyl, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, C_{1-8} alkylthio, optionally substituted benzylthio, CH_2OH, amino, NHCO C_{1-8} alkyl, $CONR^{12}R^{13}$, $CONHR^{14}$, $CH_3(CH_2)_r$-O-$(CH_2)_s$-O-, $CH_3(CH_2)_t$-O-$(CH_2)_u$-O-CH_2, and a group of Formula (II)



II

wherein

the ring B is selected from benzene, naphthalene, pyridine, furan, benzofuran, thiophene, or benzo[b]thiophene;

R^9 and R^{10} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, CH_2OH, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl, optionally substituted benzyloxy;

R^{11}, R^{12}, and R^{13} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, and optionally substituted phenyl;
R^{12} and R^{13} together with the nitrogen atom to which they are attached optionally combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkylene, wherein the C_{2-6} alkylene is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by oxygen or sulfur;

R^{14} is an amino acid residue selected from glycine, alanine, leucine, isoleucine, methionine, phenylalanine, or valine in which the carboxylate may form a carboxylic acid or a C_{1-8} alkyl ester;

R^{15} is selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, hydroxy, halo, cyano, nitro, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, C_{1-8} alkylthio, amino, NHCO C_{1-8} alkyl, optionally substituted NHCO phenyl, optionally substituted phenyl;

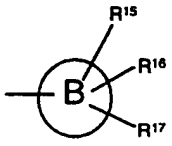
R^{16} and R^{17} are independently selected from hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, hydroxy, halo, halo C_{1-8} alkyl, optionally substituted benzyloxy;

p, r, and t are each independently selected a number consisting of 0, 1, 2, 3, or 4;

q, q', s, and u are each independently a number consisting of 1, 2, 3, 4, or 5;

m and m' are each independently a number consisting of 0, 1, or 2;

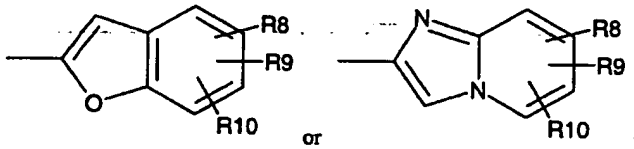
and provided that when Y is a bond or –O- and A is benzene and only one selected frm the group consisting of R^8, R^9 and R^{10} is a non-hydrogen group, then at least one selected from the group consisting of R^8, R^9 and R^{10} is selected from the group consisting of C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-8} alkoxy, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cycloalkyl, cyano, nitro, formyl, carbo C_{1-8} alkoxy, substituted phenyl, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted benzylthio, amino, NHCO C_{1-8} alkyl, $CONR^{12}R^{13}$, $CONHR^{14}$, $CH_3(CH_2)_r$-O-$(CH_2)_s$-O-, $CH_3(CH_2)_t$-O-$(CH_2)_u$-O-CH_2, and a group of Formula (II)



II

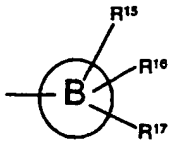
B is selected from the group consisting of benzene, wherein at least one selected from the group consisting of R^{15}, R^{16} and R^{17} is a non-hydrogen group when B is benzene, naphthalene, pyridine, furan, benzofuran, thiophene, or benzo[b]thiophene;

or when Y is a bond and A is a group of the formula



then R^8 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl, C_{1-8} alkynyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, nitro, formyl, carboxy, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8}

alkoxy, C_{1-8} alkylthio, optionally substituted benzylthio, CH_2OH, amino, NHCO C_{1-8} alkyl, $CONR^{12}R^{13}$, $CONHR^{14}$, $CH_3(CH_2)_r$-O-$(CH_2)_s$-O-, $CH_3(CH_2)_t$-O-$(CH_2)_u$-O-CH_2, and a group of Formula (II)



II; and

pharmaceutically acceptable salts and esters thereof.

2. A compound as claimed by claim 1 wherein R^1 and R^2 are each hydrogen and R^3 and R^4 are each hydrogen or methyl.
3. A compound as claimed by any one of Claims 1 through 2 wherein R^5 is hydrogen.
4. A compound as claimed by any one of Claims 1 through 3 wherein Y is a bond.
5. A compound as claimed by any one of Claims 1 through 4 wherein A is selected from the group consisting of benzene, naphthalene, thiophene, benzofuran, pyrrole, isoxazole, 4,5-dihydroisoxazole, and imidazo[1,2-a]pyridine.
6. A compound as claimed by any one of Claims 1 through 5 wherein A is selected from the group consisting of naphthalene, thiophene, benzofuran, pyrrole, isoxazole, 4,5-dihydroisoxazole, and imidazo[1,2-a]pyridine.
7. A compound as claimed by any one of Claims 1 through 4 wherein A is benzene and at least one selected from the group consisting of R^8, R^9 and R^{10} is a non-hydrogen group.
8. A compound as claimed by any one of Claims 1 through 4 wherein at least two selected from the group consisting of R^8, R^9 and R^{10} is a non-hydrogen group.
9. A compound as claimed by any one of Claims 1 through 8 wherein B is selected from the group consisting of naphthalene, pyridine, furan, benzofuran, thiophene, or benzo[b]thiophene;

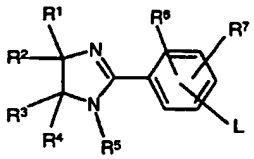
10. A pharmaceutical formulation comprising a compound according to any one of the preceeding Claims 1 through 9 or a pharmaceutically acceptable salt or ester thereof, together with a pharmaceutically acceptable carrier or diluent therefor.

11. A compound according to any one of the preceeding Claims 1 through 9 for use in the manufacture of a medicament for treating of diabetes.

12. A compound according to any one of Claims 1 through 9, for use as a pharmaceutical.

13. A compound according to any one of Claims 1 through 9, for use in the manufacture of a medicament for the treatment of a mammal for diabetes, diabetic complications, metabolic disorders, or related diseases where impaired glucose disposal is present.

14. A compound of the Formula III



III

R^1, R^2, R^3, and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^3, together with the carbon atoms to which they are attached, combine to form a C_{3-7} carbocyclic ring and R^2 and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^1 and R^2, together with the carbon atom to which they are attached combine to form a C_{3-7} spirocarbocyclic ring and R^3 and R^4 are each independently hydrogen or C_{1-8} alkyl; or

R^3 and R^4, together with the carbon atom to which they are attached, combine to form a C_{3-7} spirocarbocyclic ring and R^1 and R^2 are each independently hydrogen or C_{1-8} alkyl;

R^5 is selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl, and an amino protecting group;

L is selected from the group consisting of bromo, iodo, and trifluoromethylsulfonyloxy;

R^6 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy;

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{1-8} alkoxy, C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, C_{3-7} cyclo C_{1-8} alkyl, C_{3-7} cyclo C_{1-8} alkoxy, hydroxy, halo, carbo C_{1-8} alkoxy, halo C_{1-8} alkyl, halo C_{1-8} alkoxy, optionally substituted phenyl C_{1-8} alkyl, optionally substituted phenyl C_{1-8} alkoxy, optionally substituted phenyloxy, (tetrahydropyran-2-yl)methoxy, C_{1-8} alkyl-$S(O)_m$, optionally substituted aryl-C_{1-8} alkyl-$S(O)_{m'}$, $CH_3(CH_2)_p$-Z^1-$(CH_2)_q$-Z^2-, and Z^3-$(CH_2)q'$-Z^2;

where

Z^1 and Z^2 are each independently a bond, -O-, -S-,  , SO_2, sulphoximino, or NR^{11};

Z^3 is hydroxy, protected hydroxy, $NR^{12}R^{13}$, protected amino, SH, or protected SH;

R^{11}, R^{12}, and R^{13} are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, optionally substituted aryl C_{1-8} alkyl, and optionally substituted phenyl;

R^{12} and R^{13} together with the nitrogen atom to which they are attached optionally combine to form a heterocyclic ring comprising the nitrogen and C_{2-6} alkylene, wherein the C_{2-6} alkylene is optionally substituted with one or two C_{1-8} alkyl groups or one carbon atom of the heterocyclic ring is optionally replaced by oxygen or sulfur;

p is a number selected from the group consisting of 0, 1, 2, 3, or 4;

q and q' are each independently a number consisting of 1, 2, 3, 4, or 5;

m and m' are each independently a number consisting of 0, 1, or 2;

and pharmaceutically acceptable salts thereof.

15. A compound as claimed by Claim 1 which is selected from the group consisting of 2-[5-Bromo-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole, 2-[4-Bromo-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride, 2-[3-Bromo-2-(2-methoxyethoxy)phenyl]-4,5-dihydro-1H-imidazole Hydrochloride, 2-(5-Iodo-2-methylphenyl)-4,5-dihydro-1H-imidazole Hydrochloride, and 2-(2-Butylthio-5-nitrophenyl)-4,5-dihydro-1H-imidazole.

16. A compound as described herein above by any one of the Examples.

INTERNATIONAL SEARCH REPORT

In . tional Application No
PCT/US 00/11881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/22 A61K31/4164 A61P5/50 C07D233/20 C07D409/10
C07D233/10 C07D405/10 C07D409/14 C07D401/10 C07D233/24
C07D471/04 C07D513/04 C07D487/04 C07D498/04 C07D413/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 182 994 A (BADISCHE ANILIN- & SODA-FABRIK AG) 14 December 1973 (1973-12-14) examples 4-9,22,24-37	1
X	GB 1 229 652 A (AMERICAN HOME PRODUCTS CORPORATION) 28 April 1971 (1971-04-28) claims 1,9-13	1
X	EP 0 846 688 A (ADIR ET COMPAGNIE) 10 June 1998 (1998-06-10) claims; examples 1,13,22	1
X	GB 1 322 339 A (AMERICAN HOME PRODUCTS CORPORATION) 4 July 1973 (1973-07-04) example 1	1

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2000	13/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Van Bijlen, H

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/11881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/14 C07D403/10 C07D233/26 //(C07D471/04,235:00, 221:00),(C07D513/04,277:00,235:00),(C07D487/04,235:00,235:00), (C07D498/04,263:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 931 218 A (THEODORE S. SULKOWSKI ET AL.) 6 January 1976 (1976-01-06) examples 3,6,8,13,15,16,20-35	1
X	US 3 852 303 A (WILLIAM J. HOULIBAN) 3 December 1974 (1974-12-03) example 3	1
A	US 5 889 032 A (VIDYA BHUSHAN LOHRAY ET AL) 30 March 1999 (1999-03-30) * column 1, 7-9 *	1,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

2

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-16 (partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).
For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentionned claims

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/US 00/11881

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
FR 2182994	A	14-12-1973	DE	2219841	A	25-10-1973
			CH	579054	A	31-08-1976
			GB	1418053	A	17-12-1975
			JP	49020171	A	22-02-1974
			US	RE32154	E	20-05-1986
GB 1229652	A	28-04-1971	NONE			
EP 846688	A	10-06-1998	FR	2756560	A	05-06-1998
			AT	189816	T	15-03-2000
			AU	719145	B	04-05-2000
			AU	4765297	A	11-06-1998
			BR	9706126	A	18-05-1999
			CA	2223541	A	04-06-1998
			CN	1186074	A	01-07-1998
			DE	69701307	D	23-03-2000
			DE	69701307	T	14-09-2000
			ES	2145563	T	01-07-2000
			GR	3032715	T	30-06-2000
			HU	9702341	A	28-07-1998
			JP	10168065	A	23-06-1998
			NO	975591	A	05-06-1998
			NZ	329312	A	28-07-1998
			PL	323515	A	08-06-1998
			PT	846688	T	31-05-2000
			US	5925665	A	20-07-1999
GB 1322339	A	04-07-1973	NONE			
US 3931218	A	06-01-1976	GB	1447054	A	25-08-1976
US 3852303	A	03-12-1974	BE	746797	A	03-09-1970
			CA	939355	A	01-01-1974
			CA	970383	A	01-07-1975
			CH	530980	A	30-11-1972
			CH	531511	A	15-12-1972
			DE	2009780	A	17-02-1972
			ES	377089	A	16-12-1972
			ES	402114	A	16-11-1975
			ES	402115	A	01-11-1975
			ES	402117	A	01-11-1975
			FR	2034663	A	11-12-1970
			FR	2100576	A	24-03-1972
			GB	1306511	A	14-02-1973
			GB	1306512	A	14-02-1973
			JP	49042510	B	15-11-1974
			JP	48043120	B	17-12-1973
			SE	365218	B	18-03-1974
			SE	405249	B	27-11-1978
US 5889032	A	30-03-1999	NONE			